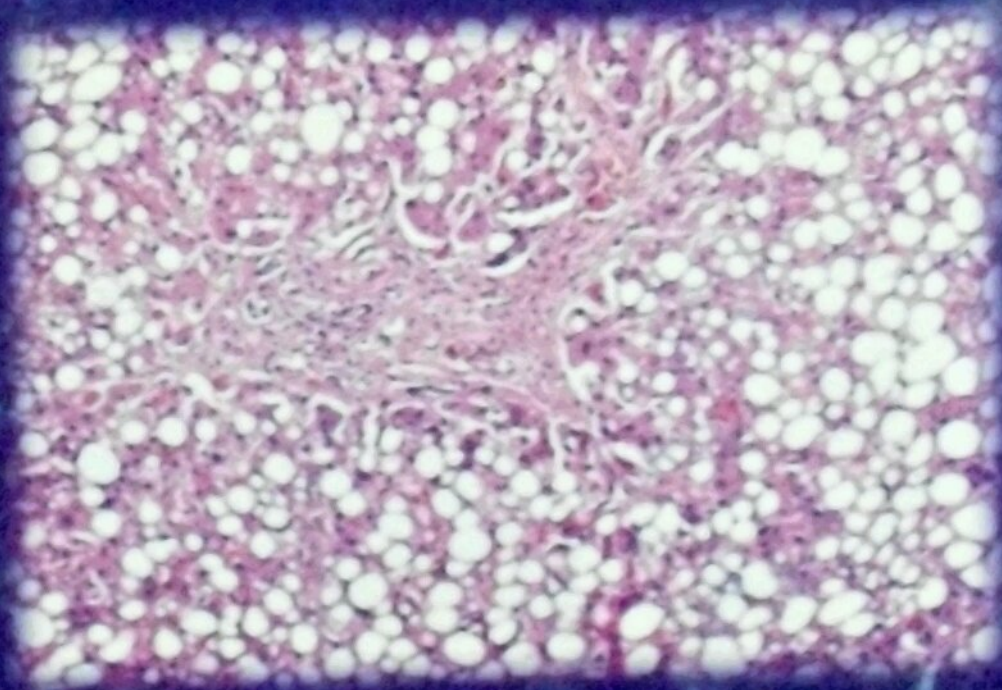


BASIC GENERAL PATHOLOGY



Ali EL-Hindawi

2010 - 2011

VISIT...

LANZAROTE
Caliente.COM

DEDICATION:

To the soul of my parents
To my beloved family
To my students

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Preface

While writing, I always feel in the depth of my soul the almighty of Allah, our great God, who gives us power, spirit, dreams, desire, hopes, perseverance and success.

Pathology is the study of diseases, dealing with their aetiology, mechanism (pathogenesis), morphological features (gross & microscopic), fate, effects and prognosis. Disease description has started several thousand years ago, and the medical papyri point to how our ancient Egyptian grandfathers had succeeded to change medical practice from a superstitious level to a category based on scientific thinking. Progressive advances in medicine were due to continuous efforts of researchers, with a bright leading role for Arabic scientists as Ibn Al Nafis. However, major understanding of many disease mechanisms has only occurred during the past few decades, for example understanding the oncogene basis of cancer evolution occurred less than 20 years ago and for this discovery Michael Bishop and Harold Varmus received the Nobel Prize in 1989. Of course, there are still many diseases that wait further understanding. The recent advances in molecular genetics and molecular pathology clarified many of the mysterious disease aspects and widely opened the gate for future therapy on a molecular gene level (gene therapy).

On an academic level, the study of pathology is elementary for clinical practice, and a good quality clinician must have good knowledge of pathology. On an applied clinical level, diagnosis of many diseases is sometimes impossible without pathological examination of specimens obtained from the diseased tissue or organ.

In this new edition, a major part of the text has been substantially updated and rewritten. I hope that this new edition will satisfy the medical reader and supplies him with simplified clear knowledge in basic pathology. I remind the reader that many of the diseases which are just mentioned by name in the book of "General Pathology", will be dealt with in more details in the book of "Systemic Pathology".

Prof. Ali El Hindawi

September 2010

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INTRODUCTION

PATHOLOGY IS THE STUDY OF DISEASE

The study is divided into:

GENERAL PATHOLOGY:

It is concerned with response of living tissues to injury i.e. what changes occur in the living cells and tissues when they are subjected to abnormal stimuli. The study of general pathology constitutes the backbone to understand systemic pathology.

SYSTEMIC (SPECIAL) PATHOLOGY:

It is the study of diseases affecting different body systems (cardiovascular system, respiratory system, alimentary tract, urinary system, nervous system...etc).

THE MAIN ASPECTS OF ANY DISEASE INCLUDE

DEFINITION and categorization of the disease.

AETIOLOGY: This includes:

- **Predisposing factors** e.g. low immunity in case of infective diseases .
- **Exciting cause:** e.g. tubercle bacilli in case of tuberculosis.
- **Pathogenesis:** it means mechanisms of development of the disease, for example . lesions of tuberculosis are mainly due to hypersensitivity , while lesions of pyogenic bacteria are due to endotoxins and lesions of diphtheria are caused by exotoxins.

MORPHOLOGICAL CHANGES (PATHOLOGICAL FEATURES): These are divided into:

- **Gross Features:** They are also called naked eye features or macroscopic features. They include all changes that can be detected by the naked eye e.g. change in size, color & consistency of the diseased organ. Gross features help in disease diagnosis & in differentiation between different lesions e.g. between abscess & tumor.
- **Microscopic Features** (by ordinary light microscopy): These are cellular and/or extracellular changes that characterize each disease e.g. detection of malignant cells, in cases of cancer & detection of bilharzia ova in cases of Bilharziasis...etc.
- **Special Microscopic Studies:** Electron microscopy & immunohistochemistry

FATE, PROGNOSIS AND COMPLICATIONS:

- **Fate** is the course of disease. It may be:
Good fate e.g. regressive disease course in mild inflammations
Bad fate: Complications (including death) .
- **Prognosis** is prediction of the disease course. It may be
Good prognosis as mild inflammations & benign tumors
Poor prognosis as in malignant tumors (cancer) and septicemia.

ROLE OF PATHOLOGY IN DIAGNOSIS OF DISEASE

TYPES OF SPECIMENS REFERRED FOR PATHOLOGICAL DIAGNOSIS

1-Biopsy: this means examination of a tissue specimen which may be:

- **Punch biopsy** e.g. from GIT, lung & bladder lesions through endoscopy (endoscopic biopsy)
- **Core biopsy** e.g. from liver, kidney, lung, mediastinum ...etc; usually guided by ultrasonography (US) or computerized tomography (CT) (guided biopsies)

- **Incisional biopsy:** This is a surgically obtained part of a lesion e.g. part of a breast mass
- **Excisional biopsy:** This is surgical excision of the whole lesion e.g. whole breast mass
- **Partial organ excision** e.g. partial nephrectomy, or subtotal thyroidectomy
- **Whole organ** as mastectomy splenectomy, total thyroidectomy, hysterectomy... etc

- 2-Autopsy:** This is examination of tissue obtained from dead bodies. It is important for:
- Detection of the cause of death. By autopsy we may discover a disease which was not diagnosed or was wrongly diagnosed during life. Thus it has a **teaching purpose**.
 - Detection of the cause of death for **medicolegal purposes** (forensic medicine)
 - Evaluation of organ state before using it for transplantation (**cadaveric transplantation**)
 - **Research studies**.

3- Frozen section examination:

- In case of biopsy and autopsy, the target is to obtain paraffin sections which is a time consuming slow technique, starting with tissue fixation in 10% buffered formalin for at least 24 hours, followed by tissue processing (taking $\pm$ extra 24 hours) through successive steps of dehydration (in ascending grades of alcohol), clearance (in xylene) and solidification (by embedding of the tissue in paraffin wax $\rightarrow$ paraffin blocks). Paraffin blocks are then cut using a microtome to get thin paraffin sections (4-5 μ thick), followed by staining with hematoxylin & eosin (H & E), special stains, or immunostains.
- On the other hand frozen section (FS) examination is used for rapid diagnosis during surgery. The biopsy is immediately transferred into a cryostat chamber, where it is frozen (within minutes) without fixation to $< 30^\circ\text{C}$. This is followed by cutting thin sections around 5-7 microns (through the microtome part of the cryostat), followed by staining & microscopic examination. Importance of FS examination is:
 - o Rapid intra-operative diagnosis, e.g. a breast or thyroid mass needs to be evaluated whether benign or malignant to determine the type of surgery.
 - o Some special stains (and immunostains) can not be performed on paraffin sections and need fresh frozen sections e.g. Sudan III (fat stain).

4- Cytology: Examination of body fluids or smears to detect any abnormal cells such as malignant cells & inflammatory cells. Examples:

- **Body fluids** as urine, CSF, effusions (pleural, pericardial & synovial), ascites, synovial & cystic fluid e.g. ovarian cysts, mammary cysts
- **Sputum**
- **Discharge** e.g. nipple discharge, conjunctival discharge.
- **Lavage fluid** e.g. bronchial lavage, bladder and/or periurethral wash.
- **Brush cytology** e.g. brush of common bile duct, bronchial and gastric brush.
- **Touch imprint cytology** e.g. imprint of the cut surface of an excised lymph node or excised breast tumor, testicular imprint...
- **Fine needle aspiration cytology (FNAC) or fine needle aspiration biopsy (FNAB)**
- **Cervicovaginal smears (PAP-smears):** These smears are stained with Papanicolaou stain
- **Bone marrow aspirate**

PREPARATION OF SPECIMENS FOR MICROSCOPIC EXAMINATION:

1- Preservation (fixation):

- **Tissue specimens (biopsy or autopsy):**
 - a) For frozen sections: **No fixation** is required and has to be avoided.
 - b) To obtain paraffin sections, the tissue is pre-fixed in 10% buffered formalin. Some tissues need special fixatives e.g. Bouin's solution for testicular biopsies.
 - c) To obtain sections for **electron microscopic examination**, the selected specimen is fixed in glutaraldehyde.
- **Cytology specimens** may not need fixation or get fixed e.g. in ethyl alcohol

2-Processing:

• Tissue specimens

- a) Frozen section examination: See above
- b) Paraffin sections: see above
- c) Bone biopsy should be decalcified (e.g. in diluted nitric acid), then processed to obtain paraffin sections as previously described
- d) Electron microscopy specimens are processed in Epon to form solid blocks, then cut into ultra-thin sections by a special microtome, followed by contrast staining in lead acetate
- **Cytology specimens:** Some specimens as FNA and nipple discharge are directly smeared on glass slides, other specimens as effusions may need centrifugation (by centrifuge or cytospin) to precipitate any cells, followed by smearing of the precipitate. Many stains can be used, as H & E, Papanicolaou (PAP) & Giemsa. Immunostains can be also done.

RESPONSE OF LIVING TISSUES TO INJURY

CAUSES OF CELLULAR INJURY:

1. **Infectious agents** including viruses, rickettsiae, bacteria and their toxins, fungi and parasites.
2. **Hypoxia** (decrease of oxygen supply) due to:
 - a) Ischemia: Reduction or loss of blood supply such as in cases of arterial thrombosis.
 - b) Inadequate oxygenation e.g. in cases of cardio-respiratory failure.
 - c) Loss of oxygen carrying capacity of the blood as in cases of anemia and carbon monoxide poisoning.
3. **Physical agents** including trauma, heat, cold, radiation and electric shock.
4. **Chemical agents** e.g. acids, alkalies, alcohol, metals as lead, some pigments & some drugs.
5. **Immunologic reactions** (hypersensitivity).
6. **Nutritional imbalances.**
7. **Genetic derangements.**

RESULTS OF INJURY OF CELLS AND TISSUES:

1. **Reversible cell injury** (degeneration): This is disturbed cell metabolism & morphology
2. **Irreversible cell injury** (cell death):
 - a) Necrosis: Cell death caused by an irritant.
 - b) Apoptosis: Cell suicide.
3. **Inflammation**
4. **Repair** (healing of tissue injury).
4. **Intracellular accumulations** (as fat, proteins, carbohydrates and pigments). These accumulations may sometimes be the cause of cell injury, but in other instances they may result from cell injury.
5. **Extracellular depositions** as **calcification** and **amyloidosis**.
6. **Cellular adaptations of growth and differentiation:**
 - a) Atrophy: Shrinkage of cell size.
 - b) Hypertrophy: Increase of cell size.
 - c) Hyperplasia: Increase of cell number.
 - d) Metaplasia: Transformation of one cell type into another.
7. **Abnormalities of cell growth:**
 - a) **Dysplasia**: Abnormal cell shape.
 - b) **Neoplasia**: Proliferation of abnormal cells $\rightarrow$ mass (tumor)
8. **Vascular disturbances** as hemorrhage, thrombosis and oedema.

INFLAMMATION

DEFINITION:

1. Inflammation is a reaction of living vascularized tissues to injury.
2. It is essentially characterized by local vascular changes resulting in formation of fluid and cellular exudates, followed by lymphatic dilatation (due to absorption of the exudates) & a local cellular reaction of tissue histiocytes (to phagocytize the inflammatory products).
3. Thus inflammation partly represents a protective response aiming at disposal of the initial cause of injury (irritants as microbes or toxins) and also disposal of the consequences of such injury (e.g. necrotic cells).
4. In spite of its protective nature, inflammation may have adverse effects (e.g. disabling pain, thrombosis and perforation of a viscus as in cases of appendicitis).
5. The suffix "itis" is added to the name of organ to denote its inflammation e.g. tonsillitis, appendicitis, colitis, hepatitis... etc.

AETIOLOGY: Injurious agents (irritants) including:

- 1-Infectious (living) irritants: Bacteria & their toxins, viruses, rickettsiae, fungi & parasites.
- 2- Physical irritants as heat, cold and radiation.
- 3-Mechanical irritants as trauma.
- 4-Chemical irritants as acids, alkalies, inorganic and organic poisons.
- 5-Irritation by exposure to antigens leading to hypersensitivity reactions

TYPES OF INFLAMMATION:

- 1-Acute inflammation: Rapid onset & short duration (days or weeks)
- 2-Chronic inflammation: Gradual onset & longer duration (several months or years)
- 3-Subacute inflammation: Grades of inflammation between acute and chronic.

1 ACUTE INFLAMMATION

LOCAL CHANGES IN ACUTE INFLAMMATION

The following changes occur in the irritated tissue:

LOCAL TISSUE DAMAGE AND RELEASE OF CHEMICAL MEDIATORS.

THE INFLAMMATORY RESPONSE: It includes

- Vascular phase → formation of inflammatory fluid exudate
- Cellular phase → formation of inflammatory cellular exudate. This phase includes:
 - Exudation of blood leukocytes, mainly phagocytic cells (neutrophils & monocytes)
 - Activation of tissue histiocytes

I) LOCAL TISSUE DAMAGE & RELEASE OF CHEMICAL MEDIATORS

At the site of injury, there are some degenerated and necrotic cells, accompanied by release of chemical substances (chemical mediators) that control the inflammatory response. These mediators may be derived from cells, plasma or bacteria (see below).

POP 3

CHEMICAL MEDIATORS

TYPES OF CHEMICAL MEDIATORS:

• Cell-Derived Chemical Mediators:

1- Vasoactive Amines:

- a) Histamine: derived from mast cells, basophils and platelets.
- b) Serotonin: derived from argentaffin cells and platelets.

2- Arachidonic Acid Metabolites:

- a) Prostaglandins. Derived from several cell types
- b) Leukotrienes derived from neutrophils.

3- Cytokines: They are produced by stimulated T lymphocytes or monocytes

- a) Cytokines derived from lymphocytes (lymphokines) include chemotactic factors, interleukin-2 (IL-2), interferons & others.
- b) Cytokines derived from monocytes (monokines) are numerous such as tumor necrosis factor (TNF) and IL-1.

4- Lysosomal enzymes derived from neutrophils and macrophages

5- Platelet Activating Factor (PAF).

• Plasma Factors:

- 1-Kinins as bradykinin
- 2-Complement system, particularly C3a and C5a components.
- 3-The clotting system, which mediates conversion of fibrinogen into fibrin.
- 4-The fibrinolytic system as plasmin, which dissolves fibrin.

• Bacterial Products.

EFFECTS OF CHEMICAL MEDIATORS:

- Vasodilatation (e.g. by histamine & prostaglandins)
- Increased vascular permeability (e.g. by histamine & prostaglandins)
- Chemotaxis (e.g. by Leukotrienes).
- Other effects as fever, leukocytosis and pain.

II) LOCAL VASCULAR CHANGES

(THE VASCULAR PHASE OF THE INFLAMMATORY RESPONSE)

THE VASCULAR CHANGES INCLUDE THE FOLLOWING SEQUENCE

- 1- Transient Vasoconstriction due to irritation of the vessel wall → stimulation of the vasoconstrictor nerves. It lasts for seconds or minutes, followed by vasodilatation →
- 2- Vasodilatation:
 - Caused by action of chemical mediators as histamine on vessel walls.
 - It affects arterioles, capillaries and venules and leads to opening of capillary bed.
 - The increased blood flow (hyperemia) → redness & hotness of the inflamed area (the flare phenomenon)
- 3- Increased Vascular Permeability & Formation of Exudate:
 - Increased vascular permeability. The mechanism includes
 - a) Endothelial cell contraction & retraction (by chemical mediators) → widening of the intercellular junctions creating gaps between the endothelial cells.
 - b) Endothelial injury which may be direct (by the irritant) or leukocyte-mediated
 - It leads to vascular leakage → fluid exudate (followed by cellular exudate). See below

↑ vascularity

4. **Vascular Stowing (Stasis):** This is local slowing of the circulation in the area:

- It is due to:
 - increased blood viscosity due to vascular leakage. It is the most important cause.
 - opening of capillary bed.
- It is an important step allowing for leukocyte exudation, since leukocytes cannot leave the blood vessels if the blood flow is rapid (see later).
- It may have an adverse effect since vascular stasis can lead to thrombosis.

THE VASCULAR CHANGES LEAD TO FORMATION OF EXUDATE

1- Formation Of The Inflammatory Fluid Exudate

Mechanism of formation & composition:

- Increased in capillary hydrostatic pressure (due to increased blood flow)
- Increased vascular permeability → leakage of fluid rich in plasma proteins particularly fibrinogen, which has a protein content $> 3 \text{ g/dl}$ and specific gravity > 1015 (around 1018). This protein-rich fluid is called exudate. It differs from the normal tissue fluid or transudate which has low protein $< 1 \text{ g/dl}$ & a lower specific gravity < 1015 .
- Reduced intravascular osmotic pressure (OP) & increased interstitial OP; both are due to loss of plasma proteins in the exudate.

The amount of fluid exudate is influenced by many factors, such as:

- Type of tissue (excessive in serous sacs & soft tissues, but scanty in bone)
- Type of irritant (e.g. excessive in case of hypersensitivity).

Functions: of exudate *enumerate?*

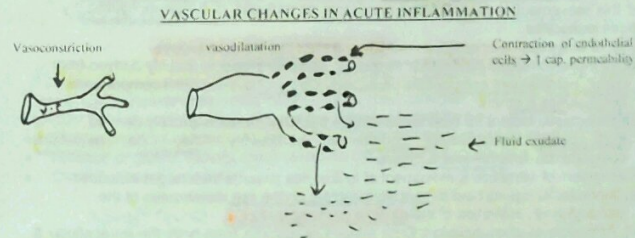
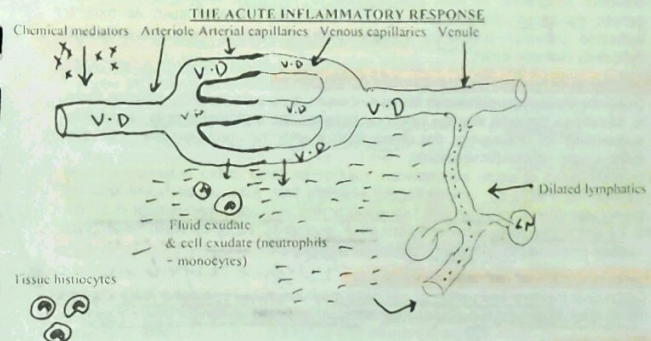
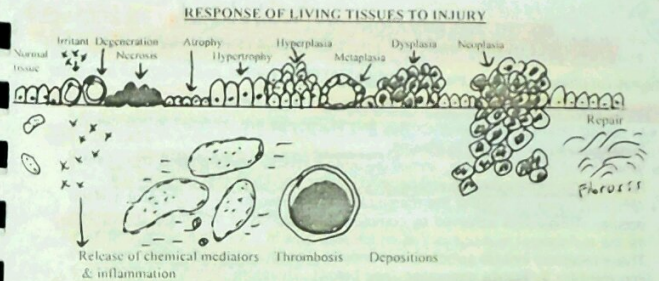
The inflammatory fluid exudate has the following important functions:

- Dilutes bacterial toxins and chemical irritants, thus minimizing their effects.
- Brings antibodies to the area as opsonins, antitoxins, bactericidins and others.
- Brings chemical mediators derived from the plasma e.g. complement
- Contains fibrinogen → fibrin (by activation of the clotting system). Functions of fibrin:
 - Helps localizing infection by surrounding the inflamed area & blocking some lymphatics.
 - Forms a network upon which phagocytic cells can move towards their target.
 - Fibrin also allows movement of proliferating fibroblasts during the process of repair.
- Supplies nutrients for the inflammatory cells.
- It finally drains the products of inflammation to restore the normal state of the tissue

Fate:

Fluid exudate is absorbed by lymphatics. If viable bacteria exist in the exudate they may cause inflammation of the lymphatic vessels (lymphangitis) and/or the draining lymph nodes (lymphadenitis). Bacteria - through lymphatics - may reach the blood causing bacteraemia, toxæmia, pyaemia or septicaemia (see later).

2- Formation Of The Inflammatory Cellular Exudate: See below



It is more blessed to give than to receive.

not migration
cell

Cell Exudate = Cellular phagocytosis
leukocytes → emigrate

III) THE INFLAMMATORY CELLULAR EXUDATE (THE CELLULAR PHASE OF THE INFLAMMATORY RESPONSE)

The cellular phase comprises the FOLLOWING STEPS

1. Margination and Pavementing of Leukocytes

- In normal flowing blood, erythrocytes and leukocytes are confined to the central (axial) column surrounded by plasma.
- When blood slowing occurs, some leukocytes (mainly neutrophils & monocytes) fall out of the central column and begin to line the endothelium (margination).
- Adhesion (pavementing) of the marginating leukocytes to the endothelial surface occurs. Adhesion is achieved by complementary adhesive molecules (receptors) on the surfaces of leukocytes and endothelial cells in a way like a key and lock. These receptors include selectins, immunoglobulins and integrins. Adhesion is very important for leukocyte emigration (see below). Therefore defective adhesion → defective emigration → poor phagocytosis → recurrent infections. There are genetic conditions characterized by poor leukocyte adhesion such as type 1 leukocyte adhesion deficiency (integrin error) & type 2 leukocyte adhesion deficiency (selectin error).

2. Emigration of leukocytes (neutrophils & monocytes)

- Once the leukocytes adhere to the endothelium, they gain stability, allowing them to insert pseudopodia into the junctions between the endothelial cells, eventually succeeding in traversing the basement membrane and escape into the extravascular space (emigration).
- In most types of acute inflammation, neutrophils (also called polymorphnuclear neutrophils, PMNs or microphages) emigrate first, followed 24 hours later by monocytes (these together with tissue histiocytes are called macrophages). It has to be noted that monocytes emigrate after neutrophils, partly because neutrophils release chemotactic (attracting) factors for monocytes.

3. Passive escape of red cells (diapedesis)

Occasional passive emigration of red cells may occur, being mechanically pushed by the emigrating leukocytes (diapedesis). No significance is known for this process.

4. Chemotaxis

- It is the directed movement of emigrating leukocytes to the site of injury. The aim of this movement is to reach the organisms or particles to be phagocytized by these leukocytes.
- Both of emigration & chemotaxis are controlled by chemotactic factors.
- a) Chemotactic factors for neutrophils include bacterial products (mainly derived from cocci), complement components particularly C5a & C3a, neutrophil components, lymphokines & others.
- b) Chemotactic factors for monocytes include bacterial products (mainly derived from bacilli), complement components particularly C5a, C3a, neutrophil components, lymphokines & others.
- Mechanism of attraction & movement of leukocytes towards their target includes:
 - a) Chemotactic agents bind to specific receptors on the cell membranes of the leukocytes → activation of the enzyme phospholipase C.
 - b) Activation of phospholipase C → release of calcium from both the intracellular & extracellular stores. This calcium activates intracellular contractile proteins (tubulin and actin) leading to active cell movement as well as extracellular contractile proteins (laminin & fibronectin) leading to passive cell movement.

Chemotaxis
directed movement

الاستين يكبريا حتى لو لم يكن دافع
* فرامعاق (phagocytosis + chemotaxis)

5. Phagocytosis

Definition & mechanism of phagocytosis: Phagocytosis is the process by which the phagocytic cells recognize then engulf abnormal particles such as bacteria, dead cells, fibrin and foreign bodies, followed by their degradation.

- Recognition & attachment of bacteria (opsonisation):** Bacteria are coated by an opsonin which is an immunoglobulin or complement factor.
- Engulfment:** Phagocytic leukocytes surround the opsonised bacteria & send cytoplasmic extensions (pseudopodia) around the bacteria or the object to be engulfed. Fusion of pseudopodia → phagocytic vacuole (phagosome). Phagosome fusion with the limiting membrane of the lysosomal granules → discharge of granule contents → phagolysosome → bacterial degradation.
- Degradation:** Killing bacteria may be done through:
 - Oxygen dependent mechanisms: Formation of hydrogen peroxide or superoxide which are bactericidal.
 - Oxygen-independent mechanisms: Lysosome hydrolyzes bacterial wall glycoproteins → a powerful bactericidal activity.

Types of phagocytic cells in acute inflammation

- Neutrophils** (polymorphnuclear neutrophils, PMNs, or microphages):
 - These are mainly attracted to & engulf cocci.
 - Some neutrophils may die due to bacterial toxins (leukocidins). Dead neutrophils may be called pus cells. These dead cells → release their proteolytic enzymes → digestion (liquefaction) of necrotic tissue and fibrin → facilitation of both of their phagocytosis by macrophages and their drainage by lymphatics.
 - Macrophages:**
 - They include emigrating monocytes, as well as tissue histiocytes.
 - Mainly attracted to & engulf bacilli, necrotic cells, fibrin, pigment & foreign bodies.
 - Other cells of the mononuclear phagocyte system** such as Kupffer cells of liver, Littoral cells of spleen and lymph nodes, microglia cells of CNS...etc
- The efficiency of phagocytosis**
- It depends on many factors as patient's immunity, dose & virulence of bacteria and nature of tissue (e.g. phagocytosis is less efficient in serous sacs).
 - In adverse conditions, bacteria may resist phagocytosis. Examples:
 - Phagocytic cells may be killed by bacterial toxins (leukocidins).
 - Some bacteria may remain alive inside macrophages (as Tubercle bacilli).

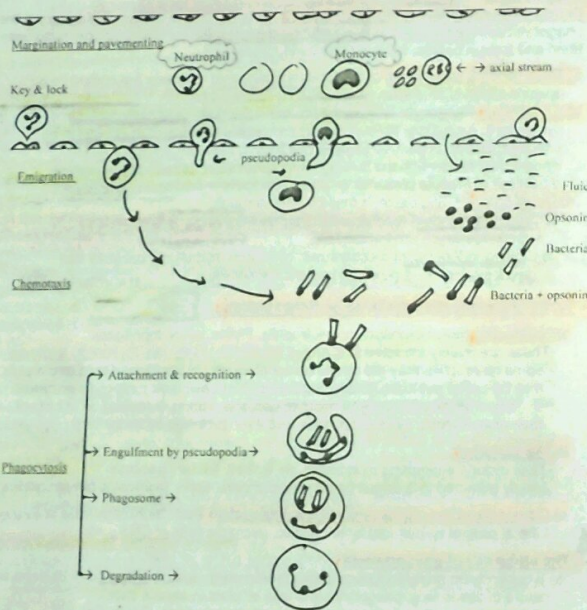
IV) ACTIVATION OF TISSUE HISTIOCYTES

Tissue histiocytes are activated and become macrophages similar to the emigrating monocytes. Macrophages can prepare the inflamed tissue for repair by:

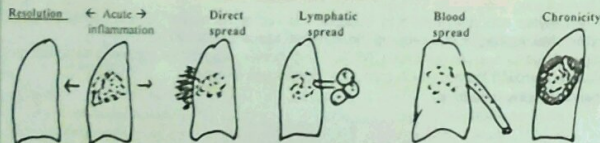
- Phagocytosis (of necrotic cells, fibrin, RBCs, foreign bodies, pigments (in addition to bacteria...)
- Release of growth factors which stimulate the process of repair.
- Other functions (see later).

* What is mechanism of phagocytosis?
* degradation?
* lymphatic oedema?

THE INFLAMMATORY CELLULAR EXUDATE



FATE OF ACUTE INFLAMMATION



chemotaxis directed movement
 release Ca^{++} phospholipase C
 Phagocytosis = 3 steps
 1. recognition
 2. engulfing
 3. degradation

SYSTEMIC (GENERAL) CHANGES IN ACUTE INFLAMMATION

1. Leukocytosis :

Increased blood leukocytes above normal ($> 10,000$ per mm^3) is due to bone marrow stimulation by leukocytosis promoting factors (cytokines), mainly IL-1 & TNF.

REMARK: Some infections as typhoid may cause leucopenia instead of leukocytosis.

2. Fever (pyrexia):

Pyrogenic factors, principally IL-1 & TNF $\rightarrow$ disturbance of the thermoregulatory center in the hypothalamus $\rightarrow$ vasoconstriction of skin vessels $\rightarrow$ fever (reduced heat loss).

LOCAL SIGNS & SYMPTOMS OF ACUTE INFLAMMATION

1. Redness due to vasodilatation & opening of capillary bed $\rightarrow$ increased blood flow.

2. Hotness due to increased blood flow. Redness & hotness are called flare.

3. Swelling (the wheal) due to accumulation of exudate (inflammatory oedema).

4. Pain: due to:

- Nerve compression by exudate
- Irritation by mediators as bradykinin and prostaglandin E2

5. Loss of function: due to pain and tissue damage.

FATE OF ACUTE INFLAMMATION

1. Resolution: This is return of the tissue to its normal state. It occurs when inflammation is limited and tissue damage is minimal. In such cases, neutralization of toxins and mediators, phagocytosis and drainage of the exudate by lymphatics is not accompanied by healing. Example resolution of lobar pneumonia.

2. Regression and healing: Inflammation subsides (as described above), but there is tissue damage which is gradually repaired (see chapter II).

3. Progression and spread: With weak immunity, bacteria may spread:

- Direct spread causing extension and widening of the inflammatory field.
- Lymphatic spread causing lymphangitis and lymphadenitis.
- Blood spread which may lead to serious effects as septicaemia.

4. Chronicity: This occurs if the injurious agent could not be eliminated completely.

TYPES OF ACUTE INFLAMMATION

1. Suppurative (purulent, septic or pyogenic) inflammation: Characterized by pus formation. Suppurative inflammation may be:

- a) Localized as abscess, boil and carbuncle
- b) Diffuse as cellulitis, suppurative appendicitis & diffuse septic peritonitis.

2. Nonsuppurative types:

- a) serous
- c) serofibrinous
- e) pseudomembranous
- g) necrotizing
- b) fibrinous
- d) catarrhal
- f) hemorrhagic
- h) allergic

chemotaxis is movement of cells
 mechanism of vascular changes
 increase blood viscosity
 3. Leukocytes are engulfed by lymphocytes

White Knight Lane

I - SUPPURATIVE INFLAMMATION

(Septic, Purulent or Pyogenic Inflammation)

Definition: Acute inflammation characterized by pus formation (liquefactive necrosis).

Caused by pyogenic organisms as *Staphylococcus aureus*, *Streptococcus hemolyticus*, gonococci, pneumococci and others.

Mechanism (pathogenesis) of pus formation:

1. Pyogenic organisms cause.
 - a) Remarkable **necrosis** to extend damage
 - b) Attraction of a huge number of **neutrophils**
 - c) Death of many neutrophils due to high virulence of the bacteria.
2. Dead neutrophils (**pus cells**) release their **proteolytic enzymes** → liquefaction of necrotic tissue & fibrin. The liquefied material mixed with pus cells & fluid exudate form a turbid creamy fluid called **pus**.

Composition of pus:

- Fluid exudate without fibrin (liquefied).
- Cells: A large number of pus cells, neutrophils, some macrophages & some RBCs
- Necrotic fragments (**sloughs**) and liquefied necrotic tissue.
- Bacteria and bacterial pigments which may be yellowish (as in staphylococcal infections) or greenish (as in pyocyanous infections).

Characters of pus:

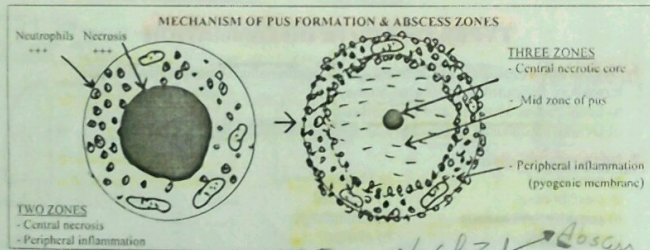
Pus caused by *Staphylococcus aureus* infection is an exudative fluid characterized by:

- **Creamy thick** (due to excess nucleic acids, liquefied fibrin & liquefied necrotic tissue)
- **Non-coagulable** (no fibrinogen)
- **Odorless & alkaline** (pH of necrotic cells is alkaline)
- **Yellowish** due to bacterial pigments & hemoglobin-derived pigments.

Pus of other types of bacteria differs a little e.g. it may be thin and sanguinous (rich in blood) in case of streptococcal infection or greenish in case of pyocyanous infections.

Types of suppurative inflammation:

1. **Localized:** Commonly caused by *Staphylococcus aureus* which produce coagulase enzyme → fibrin deposition → localization. The most common forms of localized suppurative inflammation are: a) **Abscess**, b) **Boil (furuncle)**, c) **Carbuncle**.
2. **Diffuse:** Caused by *Streptococcus haemolyticus* which produce hyaluronidase (spreading factor) & streptokinase (fibrinolysin) which dissolves fibrin. The most common examples are: a) **Cellulitis**, b) **Suppurative appendicitis**, c) **Diffuse septic peritonitis**.



Local

1. ABSCESS

Definition:

A type of localized suppurative inflammation characterized by a cavity containing pus.

Aetiology: It is commonly caused by *Staphylococcus aureus* infection.

Sites: It is most common in the subcutaneous tissues, but can occur in any organ (lung, liver, brain, bone, kidney, testis, ovary... etc)

Pathological Features:

1. **Early:** two zones can be recognized:
 - a) A central zone of necrosis
 - b) A peripheral zone of inflammation showing many neutrophils, pus cells, macrophages, dilated capillaries and fibrin.
2. **Later:** progressive liquefaction starts at the margin of necrotic tissue → three zones:
 - a) A central necrotic core
 - b) A mid zone of pus
 - c) The peripheral zone of inflammation (now called the pyogenic membrane).
3. **Further enlargement:** The central necrotic core may disappear by further liquefaction and the abscess may enlarge if the bacteria cause further necrosis and liquefaction.
4. **Fate of abscess:**
 - a) Small abscess: Pus is may be absorbed, followed by healing.
 - b) Large abscess: Since absorption of pus occurs at a very slow rate, a big abscess (if not surgically incised) → pointing & rupture (spontaneous evacuation) → healing.

Complications of abscess:

1. **Spread of infection:**
 - a) Direct spread leads to abscess enlargement.
 - b) Lymphatic spread leads to lymphangitis and lymphadenitis.
 - c) Blood spread may lead to:
 - Toxaemia: Bacterial toxins circulating in the blood.
 - Septicaemia: large numbers of virulent bacteria & their toxins circulating in blood. Commonly fatal.
 - Pyaemia: Septic venous thrombi (septic thrombophlebitis) may develop close to the abscess. If these thrombi become fragmented → circulating septic emboli → multiple small abscesses in distant organs. These small abscesses are called pyemic abscesses and the whole process is called pyemia

2. Complications of evacuation and healing:

- a) **Ulcer:** It is a local defect within a surface (skin, mucosa...). It is due to separation of inflammatory necrotic tissue. If infection persists → defective healing → **chronic ulcer**
- b) **Sinus:** It is a blind ended tract between a deep abscess and the surface, e.g. a perianal abscess may cause sinuses on the abdominal wall. If infection persists it remains as a **chronic sinus**
- c) **Fistula:** Evacuation of a deep abscess may result in a tract communicating between two surfaces or hollow organs. This double ended tract is called fistula. Ano-rectal fistula complicating a perianal abscess is an example. If infection persists, it changes into a **chronic fistula**
- d) **Keloid** (see chapter II)

e) Hemorrhage e.g. hemoptysis when a lung abscess opens into a bronchus.
f) Rupture: e.g. brain abscess into ventricles & right hepatic lobe abscess into base of right lung

3-Chronicity: If the abscess is neither evacuated spontaneously nor surgically, it gets surrounded by fibrosis and becomes a chronic abscess. Pus dries and dystrophic calcification may occur. Examples: a) Chronic breast abscess: May be clinically mistaken for a tumor. b) Chronic lung abscess.

4-Other complications:

a) Putrefaction → gangrene (e.g. putrefaction of a lung abscess by saprophytic bacteria).
b) Compression effects: e.g. in case of brain abscess → increased intracranial tension & liver abscess → obstructive jaundice.

2 FURUNCLE (BOIL)

Staphylococcal infection of the hair follicles (folliculitis) is common in the face of males and axilla of females. Folliculitis may regress, or progress to suppuration → furuncle (boil) = small abscess related to the hair follicle. Furuncles may be multiple (furunculosis).

3 CARBUNCLE

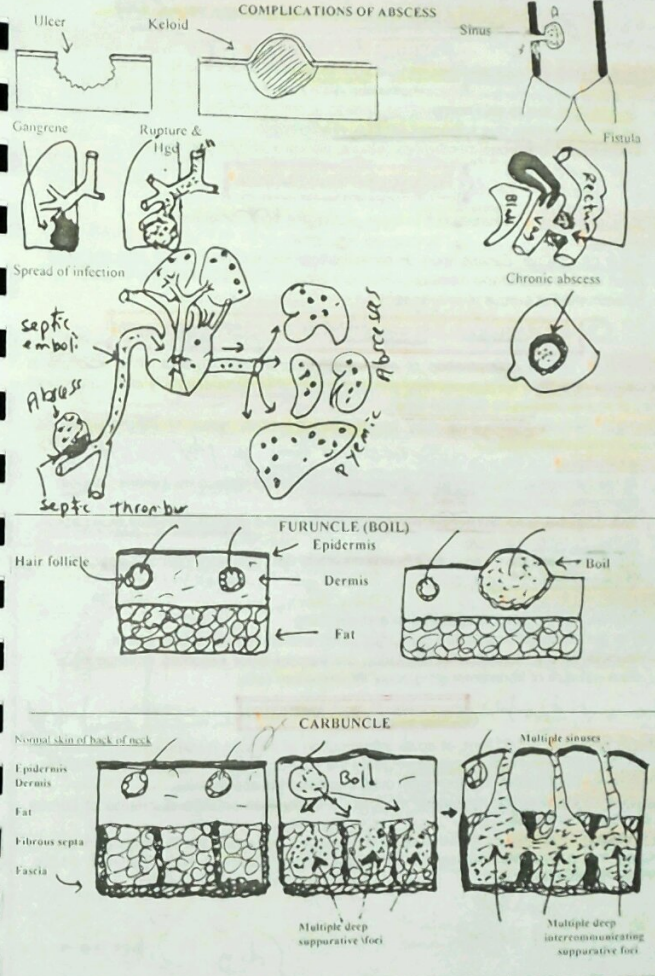
- A special type of localized suppurative inflammation characterized by multiple communicating deep subcutaneous abscesses, opening on skin by multiple sinuses.
- It only occurs in special sites where the skin and subcutaneous tissues are thick and tough due to dense fibrous septa that extend between the deep fascia and the dermis; thus dividing the subcutaneous fat into compartments, therefore infection reaching these multiple compartments leads to multiple suppurative foci. Sites of carbuncle include back of neck, scalp & buttocks.
- More common in diabetics (low immunity). It starts as a boil then progress → carbuncle.

Diffuse

4 CELLULITIS

Cellulitis is an acute diffuse suppurative inflammation, more common in diabetics. The differences between cellulitis and abscess are listed in the following table:

ABSCESS	CELLULITIS
- Localized suppurative inflammation. - Caused by <i>Staphylococcus aureus</i>. - Bacteria → coagulation → localization.	- Diffuse suppurative inflammation. <i>Streptococcus haemolyticus</i>. - Bacteria → fibrinolysin & hyaluronidase → diffusion.
Occurs in any organ or tissue, but is most common in subcutaneous tissue.	Occurs in loose connective tissues as subcutaneous tissues, areolar tissue of orbit, scrotum & pelvis.
- Pus is characterized by: - Thick due to the presence of large amount of liquefied fibrin. - Contains few erythrocytes. - Contains few sloughs (necrotic tissue).	- Pus is characterized by: - Thin, due to less amount of liquefied fibrin (fibrinolysin antagonizes fibrin deposition). - Sanguineous (contains many RBCs). - Contains many sloughs due to extensive necrosis.
Spread of infection is less common.	Spread of infection is more common.



It is more blessed to give than to receive.

II- NON SUPPURATIVE INFLAMMATION

1. SEROUS INFLAMMATION

Characterized by excessive serous fluid poor in fibrin.

Examples:

- Skin blisters due to skin burns.
- Epidermal vesicles due to herpes simplex viral infection.
- Inflammation of serous membranes (pleura, pericardium and peritoneum).

2. FIBRINOUS INFLAMMATION

Characterized by an exudate rich in fibrin, with a little fluid component.

Examples:

- Lobar pneumonia: Excess fibrin → consolidation (hepatization) of the affected lobes.
- Adult hyaline membrane disease.
- Inflammation of serous membranes.

3. SEROFIBRINOUS INFLAMMATION OF SEROUS MEMBRANES:

Definition: This is inflammation of serous membranes rich in both fluid exudate & fibrinogen. The fluid component may predominate (wet or serous type). Fibrin component may predominate (dry or fibrinous type).

Remark: Serous membranes may be affected by other types of inflammation e.g. suppurative inflammation.

Gross Picture:

- At the beginning, the visceral and parietal layers of the serous membrane appear hyperemic and oedematous. Then they become thickened, reticulated, opaque and grayish, particularly in case of the dry (fibrinous) type.
- The serous sac cavity contains abundant serous fluid (effusion) particularly in case of the wet (serous) type.

Microscopic Features:

- Serosal cells undergo degeneration and shedding.
- The subserosa shows dilated capillaries, fibrin and acute inflammatory cells.
- In case of dry (fibrinous) inflammation the serosal layer becomes covered by a thick network of fibrin entangling acute inflammatory cells.

4. CATARRHAL INFLAMMATION

Characteristics: A mild form of acute inflammation of mucous membranes characterized by an exudate mixed with mucus secreted by the irritated mucous membrane.

Examples: Catarrhal rhinitis (common cold) and catarrhal appendicitis.

Gross Picture: Swollen hyperemic mucosa; first dry then pours a discharge of serous fluid mixed with mucus.

Microscopic Picture: Epithelial cells of the mucosa are swollen and vacuolated due to excess mucin (mucoid degeneration). The submucosa shows dilated capillaries, PMNs, macrophages and fibrin.

dry (mild), to wet (moist) reaction

5. PSEUDOMEMBRANOUS (MEMBRANOUS) INFLAMMATION

Characteristics & pathogenesis:

- A severe form of acute inflammation of mucous membranes characterized by replacement of the normal mucous membrane by a false membrane composed of necrotic tissue & fibrin.
- Virulent bacteria secreting exotoxins as *Mycobacterium diphtheriae* → mucosal necrosis and marked submucosal inflammation → false membrane composed of necrotic mucosal patches and excessive fibrin.

Examples: Diphtheria & Bacillary dysentery.

Gross Picture: The original mucous membrane is replaced by another (false) membrane, which appears yellowish gray, thick and adherent. If forcibly removed, it leaves a bleeding surface and is reformed rapidly.

Microscopic Picture: The false membrane consists of necrotic patches, fibrin, bacteria and acute inflammatory cells. The underlying submucosa shows dilated capillaries, fibrin and acute inflammatory cells (PMNs and macrophages).

6. HAEMORRHAGIC INFLAMMATION

Characterized by excess RBCs within the exudate due to associated vascular damage.

Example: Small pox & hemorrhagic cystitis

7. NECROTIZING INFLAMMATION

Characterized by: extensive necrosis in association with inflammation.

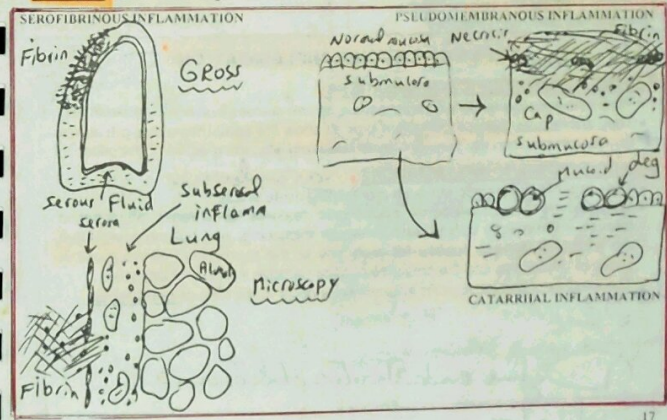
Example: Cancrum oris.

8. ALLERGIC INFLAMMATION

The underlying cause of inflammation is hypersensitivity.

Characterized by many eosinophils.

Examples: Urticaria, allergic rhinitis and bronchial asthma.



CHRONIC INFLAMMATION

PATHOLOGICAL FEATURES OF CHRONIC INFLAMMATION

- Chronic inflammation lasts for a long duration.
- It may follow acute inflammation due to failure of defense mechanisms.
- It may start chronic by gradual onset (not preceded by an acute phase) due to one or more of the following:
 - Infection with resistant organisms e.g. tuberculosis. T.b.
 - Non-living irritants as foreign bodies e.g. silicosis & asbestosis (inhalation of silica or asbestos particles into lungs)
 - Development of autoimmunity e.g. rheumatoid arthritis. → attack → chronic joint
- The inflammatory response basically resembles that of acute inflammation. The main differences between acute & chronic inflammation are listed in the next table;

ACUTE INFLAMMATION	CHRONIC INFLAMMATION
- Rapid onset and short duration. - Marked vasodilatation	- Gradual onset & long duration. - Less marked vasodilatation. Endarteritis obliterans may occur (thickening & narrowing of small blood vessels) - Usually scanty fluid exudate. - Main inflammatory cells: Macrophages, lymphocytes, plasma cells and giant cells - Fibrosis occurs.
Variations in acute inflammatory cells: - Eosinophils appear in allergic inflammation - Neutrophils may be few or absent in cases of infection with bacilli as typhoid - Lymphocytes & plasma cells may be the predominant cells in viral infections	

TYPES OF CHRONIC INFLAMMATION

1- CHRONIC NONSPECIFIC INFLAMMATIONS:

- They usually follow acute inflammation, e.g. chronic abscess & chronic pyelonephritis.
- They are termed "nonspecific" since they all show the same microscopic features (chronic inflammatory cells, fibrosis, vascular thickening, etc.) irrespective of the cause.

2- CHRONIC SPECIFIC INFLAMMATIONS:

- They usually start chronic without a pre-existing acute phase.
- They exhibit the conventional microscopic features of chronic inflammation (chronic inflammatory cells, fibrosis, vascular thickening, etc) but moreover there are additional features specific for each type as the presence of bilharzia ova in cases of bilharziasis and the presence of silica particles in cases of silicosis.
- The majority of chronic specific inflammations occur in the form of **granulomas**.

Define endarteritis obliterans?

Thickening + narrowing of blood vessels in chronic inflammation

Causes: Radiation, syphilis, poisoning

DEFINITION & PATHOLOGICAL CHARACTERISTICS:

- A particular form of chronic inflammation characterized by nodular collections of macrophages with a variable mixture of lymphocytes, plasma cells, giant cells & sometimes neutrophils.
- The macrophages commonly change into larger eosinophilic cells. These modified macrophages are called epithelioid cells.
- Some granulomas may exhibit central necrosis.
- Granulomas often represent type IV hypersensitivity, where stimulated T lymphocytes release lymphokines that attract large numbers of macrophages.

TYPES OF GRANULOMAS:

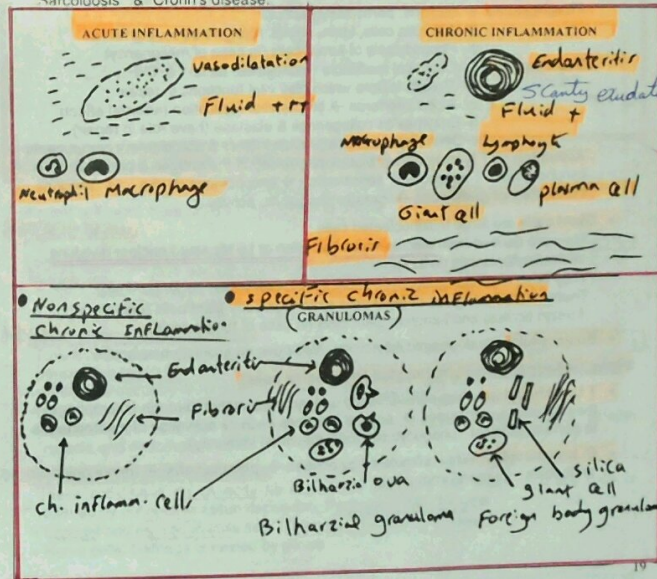
1- Infectious granulomas: Most of these granulomas are necrotizing. Examples:

- Bacterial as tuberculosis, brucellosis, syphilis, leprosy and cat-scratch disease.
- Parasitic as schistosomiasis (bilharziasis).
- Fungal as coccidiomycosis, cryptococcosis and histoplasmosis.

2- Foreign body granulomas: Mostly non-necrotizing granulomas. Examples:

- Silicosis
- Foreign body granulomas around surgical sutures, or other foreign bodies when trapped in a tissue as pieces of glass, metal, wood, etc.

3- Granulomas of unsettled aetiology: Mostly non-necrotizing granulomas. Examples: Sarcoidosis & Crohn's disease.



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TYPES & FUNCTIONS OF INFLAMMATORY CELLS

According to type of inflammation:

1-Acute inflammatory cells

- **Neutrophils** (microphages, polymorphonuclear neutrophils). They are most numerous in pyogenic infections. Dead neutrophils are called **pus cells**.
- **Macrophages**. They are derived from blood monocytes & tissue **histiocytes**.
- **Possible variations** e.g.:
 - Eosinophils in allergic inflammation
 - Lymphocytes & plasma cells in viral infections
 - Paucity of neutrophils in bacillary infections as typhoid

2-Chronic inflammatory cells

- **Lymphocytes**. (T & B lymphocytes)
- **Plasma cells** (derived from stimulated B lymphocytes)
- **Macrophages**
- * **Giant cells**. They are most commonly seen in granulomas.

According to function

1-Phagocytic cells:

- **Neutrophils** mainly engulf cocci
- **Macrophages** have several functions:
 - **Phagocytosis**: a- Bacteria, particularly bacilli.
b- Necrotic cells, fibrin, debris, foreign bodies, pigments.
c- Phagocytosis of tumor cells (in case of malignancy)
 - **Secretion of**: a- Chemical mediators (monokines) as IL-1 & TNF
b- Growth factors which play vital functions in repair
c- Alpha interferon → blocks viral replication (antiviral effect)
d- Enzymes as collagenase & elastase (have role in repair)
e- Others as some coagulation factors & complement components

• **Activation of T lymphocytes**: Macrophages engulf the antigen & present it to T lymphocytes → T lymphocyte sensitization → lymphokines → immune functions.

• **Formation of giant cells** → greater phagocytic activity

- **Giant cells** are large multinucleated cells
 - They are derived from macrophages by **fusion** or by **repeated nuclear divisions** without cytoplasmic division.
 - They have a greater phagocytic capacity and can engulf larger particles.
 - There are several types of giant cells as foreign body giant cells (engulfing foreign bodies) and Langhan giant cells (in case of tuberculosis)

- **Eosinophils**: Weak phagocytic activity. Also have an antihistamine action

2-Immunological cells (lymphocytes and plasma cells):

- **T Lymphocytes**: when sensitized (by antigen presentation through macrophages) they secrete lymphokines → several functions such as activation of macrophages to perform efficient phagocytosis (cell mediated immunity)
- **B lymphocytes**: When stimulated by antigen → **plasma cells** → immunoglobulin antibodies (humoral immunity).

① P.11 Regression & Healing do 192
② P.13 Kulooid

CHAPTER II

REPAIR (HEALING)

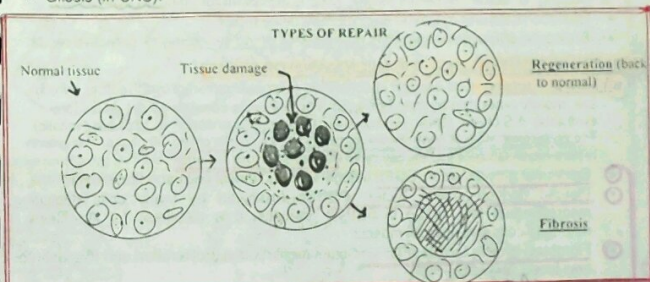
= replace damaged by new healthy one

DEFINITION:

Repair is the replacement of a damaged tissue by a new healthy one.

TYPES OF REPAIR:

1. **Regeneration**: Replacement of the damaged tissue by tissue of the same type
2. **Healing by connective tissue deposition**
 - **Fibrosis** (scarring): in any part of the body except CNS
 - **Gliosis** (in CNS).



WHAT DETERMINES THE TYPE OF REPAIR?

The type of repair is mainly determined by the type of damaged cells, because the different cell types have different capacities to divide:

1. Labile cells:

These cells continuously divide actively through life to replace cell loss. They have short G0 phase. Complete regeneration is possible following their injury. Labile cells include:

- Surface epithelia of skin and mucous membranes.
- Hematopoietic and lymphoid tissue.

2. Stable cells (quiescent cells):

These cells have a limited capacity of division. They remain in the G0 phase for long periods but retain the capacity to enter the mitotic cell cycle if in need. Following injury, repair may occur by regeneration or by fibrosis. Stable cells include:

- Parenchymal cells of the glandular organs (liver, kidney, pancreas...etc)
- Mesenchymal cells as **fibroblasts**, **astrocytes**, **osteoblasts**, **chondroblasts**, smooth muscle and endothelial cells.

3. Permanent (non-dividing) cells:

These cells have no capacity for division in postnatal life. Injury to these cells is repaired by connective tissue deposition. Permanent cells include:

- **Skeletal** and **cardiac muscle cells**. Damage is healed by fibrosis.
- **Nerve cells**. Damage is healed by gliosis

FACTORS AFFECTING REPAIR:

1- FACTORS AFFECTING EFFICIENCY & TYPE OF REPAIR:

a) Local Factors:

- Type of damaged cells (labile, stable or permanent).
- Blood supply e.g. local ischemia → defective repair.
- Persistent infection or presence of foreign bodies → delays repair.
- Extent of tissue damage

b) General (Systemic) Factors:

- Age: Repair is better in younger ages.
- Nutritional deficiencies including proteins, vitamin C (& vitamin D in case of bone healing) & some minerals as zinc (zinc is important for collagen synthesis).
- Glucocorticoid and cytotoxic drug therapy delay repair
- Endocrine diseases as diabetes mellitus & Cushing syndrome → defective repair.

2- FACTORS CONTROLLING THE MECHANISM OF REPAIR

a) **Growth Factors:** Cell division is controlled by stimuli called growth factors which are mostly produced by macrophages. The cell cycle consists of G1 phase (pre-synthesis) → S phase (DNA synthesis) → G2 phase (premitotic) → M phase (mitotic). The physiologic state of non-division of the quiescent cells is called G0 phase. The growth factors recruit G0 cells into the cell cycle. Growth factors include

- Epidermal growth factor (EGF): Mitogenic for epithelial cells and fibroblasts.
- Platelet derived growth factor (PDGF): Produced by many cells (including macrophages) and stored in platelet granules. It is mitogenic for fibroblasts, neuroglia cells and smooth muscle.
- Fibroblast growth factors (FGFs): Stimulate fibroblast proliferation and formation of new blood vessels.
- Transforming growth factor alpha (TGF-α): Stimulates fibroblast proliferation (stimulatory effect) and also enhances collagen degradation (inhibitory effect).
- Transforming growth factor beta (TGF-β): Stimulates fibrogenesis (stimulatory effect). It has also a growth inhibition action (inhibitory effect).
- IL-1, TNF & other macrophage derived growth factors.

Remark:

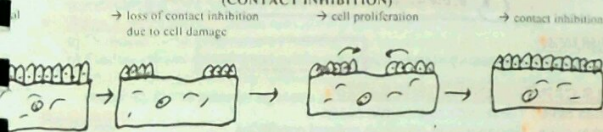
b) Cell to cell interactions (contact inhibition):

- Cells of normal un-injured tissues are in intimate contact. This contact prevents their un-needed division. The mechanism of this growth inhibition is not clear, but it involves inhibitory signals, surface receptor interactions and growth inhibition factors (chalones) that suppress mitosis (as TGF-β).
- Tissue damage → cell loss → loss of contact inhibition → stimulation of the cells to divide until they establish contact again (by the end of repair) leading to contact inhibition once more.

c) Cell to matrix interactions:

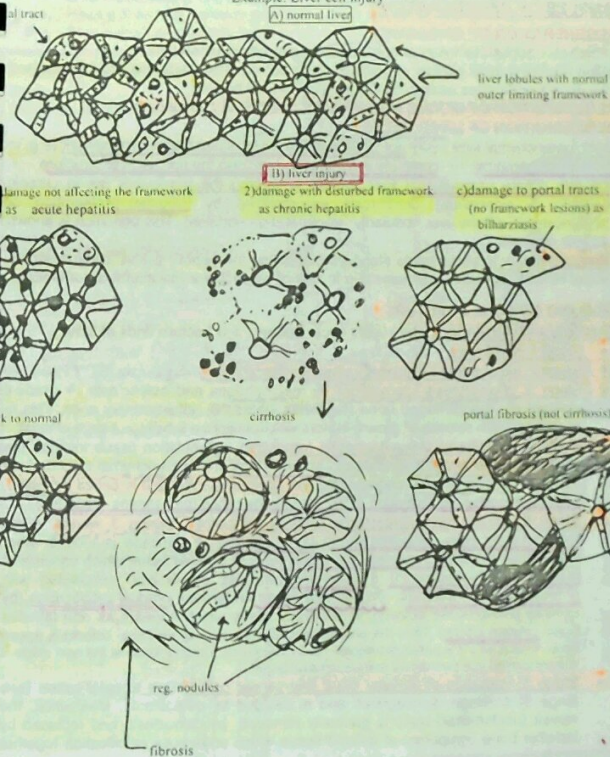
- Extracellular matrix (ECM) proteins (glycoproteins) include fibronectin & laminin → important roles influencing cell migration, proliferation, differentiation & adhesion.
- Abnormalities in these interactions → serious effects, e.g. chronic liver disease disturbing the extracellular framework → abnormal repair → cirrhosis (see later).

CELL TO CELL INTERACTIONS (CONTACT INHIBITION)



CELL TO MATRIX INTERACTIONS

Example: Liver cell injury



It is more blessed to give than to receive.

- ① Define Callus, ② mechanism of formation of Callus
③ Discuss causes of defective Callus formation

REPAIR BY REGENERATION

DEFINITION:

Replacement of the damaged tissue by tissue of the same type

CELLS CAPABLE OF REGENERATION

- 1-Labile cells: These cells regenerate easily.
- 2-Stable cells: Regeneration occurs in optimal conditions
- 3-No regeneration of permanent cells

EXAMPLES OF REGENERATION:

1. REGENERATION OF EPIDERMIS:

- a) Abrasion: Superficial injury of epidermis → complete regeneration.
- b) Skin wound: It means injury of epidermis and dermis. The epidermis regenerates and the dermis undergoes healing by fibrosis (see wound healing)

2. REGENERATION OF MUCUS MEMBRANES OF GIT and urinary tract

3. REGENERATION OF LIVER CELLS:

- Mild parenchymal liver injury not disturbing the extracellular hepatic framework (e.g. in acute viral hepatitis) → complete regeneration restoring the normal liver structure
- Chronic diffuse parenchymal liver disease disturbing the framework (as in chronic hepatitis & alcoholism) → fibrosis accompanied by irregular proliferation of hepatocytes → diffuse liver nodularity (regeneration nodules). This condition is known as liver cirrhosis.
- Remark: Injury to portal tracts alone, not affecting the hepatic (as in bilharziasis) → portal fibrosis. This is not cirrhosis due to lack of parenchymal structural disturbance).

4. HEALING OF BONE FRACTURE:

Mechanism of Healing: The events occur between the fracture ends of bone

- Stage 1: hematoma → release Growth factors
- Stage 2: inflammatory exudate (traumatic inflammation) → due to trauma
- Stage 3: phagocytosis (demolition) by macrophages and osteoclasts → gradual removal of the damaged bone fragments, blood & inflammatory cells. This is associated with release of growth factors which control the subsequent steps of repair
- Stage 4: granulation tissue formation (procallus): granulation tissue invades the area within one week. It consists of capillary loops and mesenchymal cells derived from the periosteum and endosteum. This granulation tissue is called procallus, since it precedes the formation of true hard bony callus (pro- means precedes)
- Stage 5: woven bone & cartilage (provisional callus). During 3 weeks, some mesenchymal cells differentiate into chondroblasts → cartilage islands & other mesenchymal cells differentiate into osteoblasts → osteoid tissue which consists of bone matrix (osseomucin) & collagen and lacks calcification associated with gradual loss of capillaries. This osteoid tissue undergoes gradual calcification (by alkaline phosphatase activity) → osseous tissue which appears as non lamellar bone (woven bone). Thus the provisional callus consists of cartilage, osteoid & woven bone. That is why it is called provisional (which means temporary), since at the next stage it is transformed into permanent mature lamellar bone
- Stage 6: formation of lamellar bone (permanent callus) Due to calcification (see stage 5) cartilage disintegrates and is invaded by osteoblasts. Meanwhile, the woven (nonlamellar) bone is gradually removed by osteoclasts and replaced by lamellar bone composed of osteoid tissue which undergoes calcification together

- ① Discuss repair of nervous damage — called a scar
② Discuss repair of peripheral nerve injury — peripheral

with deposition of collagen bundles which are arranged in orderly lamellar fashion (concentrically around blood vessels → formation of Haversian system)

- Stage 7: remodeling. Callus remodeling (adjustment) occurs through:
 - a) Removal of the unnecessary internal & external callus (by osteoclastic activity)
 - b) Further adjustment of the intermediate callus (to give it optimal size, strength and lamellar property) by further osteoblastic and osteoclastic activity, in response to mechanical stresses along lines of weight bearing.

Remarks:

- Callus in Latin means hard. However, the term was used to describe tissue uniting fracture ends, regardless of its consistency. Sometimes, the procallus is described as soft callus, while the provisional and permanent callus are described as hard callus.
- Healing of bone (≥ 4 weeks) may be so perfect that the fracture site may not be identified.
- Bone marrow regenerates inside the medullary canal

MECHANISM OF BONE HEALING

Stages 1, 2 & 3

(hematoma, traumatic inflamm & demolition)

macrophage
osteoclast
release Growth factors

Stage 4: granulation tissue (procallus)

- Since it precedes formation of true hard bone
- within week
- derived from periosteum & endosteum
- capillary loops & mesenchymal cells

Stage 5: woven bone & cartilage (provisional callus)

= Cartilage + osteoid + woven bone
= temporary (non lamellar)

displaced B.V.
Stage 6 lamellar bone (permanent callus)

Stage 6: woven bone & cartilage (provisional callus)

Woven non lamellar gradually remodelled

by osteoclasts
replaced by lamellar
new osteoid + capillary

Stage 7: remodeling

by osteoclasts
body adjusted by osteoclast

DEFECTIVE BONE HEALING

Soft tissue interposition

Malalignment

Fibrous union (false joint)

Tumor

Infection

bone repair → perfect

5 Local + 4 General

Causes of Defective (Imperfect) Bone Healing & failure of bony union:

Some conditions may lead to nonunion, weak union or fibrous union (pseudoarthrosis):

A) Local factors:

- Inadequate immobilization or malalignment
- Pathological fracture e.g. due to bone lump or osteoporosis
- Soft tissue interposition between the fracture ends
- Ischemia
- Infection

B) General factors as

- old age
- Nutritional deficiencies
- Glucocorticoid therapy, e.g. Cushing's
- Diabetes mellitus

5-HEALING OF DAMAGE TO NERVOUS SYSTEM

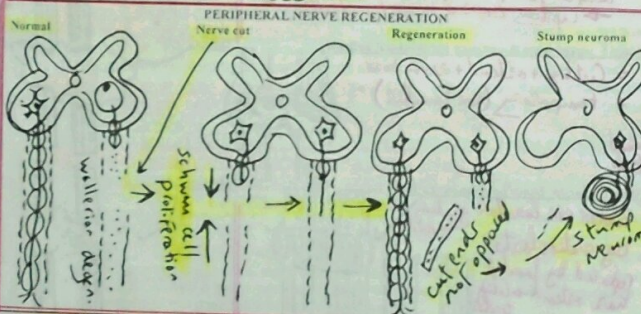
- Injury of a peripheral nerve** may be regenerated since nerve cells are preserved.

Mechanism of regeneration of Peripheral Nerve Cut:

Nerve injury leads to:

- Axonal degeneration** of the nerve cells, which appear swollen with eccentric nuclei & loss of Nissl granules (chromatolysis). They recover within three weeks.
- Wallerian degeneration** (Within 48 hours) the myelin and axis cylinder of the nerve become disintegrated. These changes affect the nerve fibers distal to the point of section & proximally up to the first node of Ranvier.
- Schwann cells** resist injury. Together with macrophages they act as phagocytic cells engulfing the products of Wallerian degeneration. They also proliferate from both the distal segment and proximal stump → integrated neurilemmal tube.
- Growth of axis cylinders.** They are secreted by the alive nerve cells. They grow inside the integrated neurilemmal tube at a rate of about 1 mm/day.
- Myelin sheath formation** around the growing axons is the final stage.

Traumatic Neuroma (Stump or Amputation Neuroma): It is a complication of nerve healing occurring if the two ends of the nerve are not opposite each other. If the nerve is severed, the distal nerve segment as in case of amputation. In these cases the proliferating Schwann cells and neurofilaments mix together forming a painful mass called traumatic neuroma or amputation neuroma (stump neuroma).



- Damage of central nervous system:** Damage to nerve cells within the CNS (brain & spinal cord) can never be regenerated, since nerve cells cannot divide. Repair starts by phagocytosis of dead tissue (by macrophages & microglia cells) then laying down a special type of connective tissue formed by astrocytes called *glia*.

Tricky

HEALING BY FIBROSIS (Granulation)

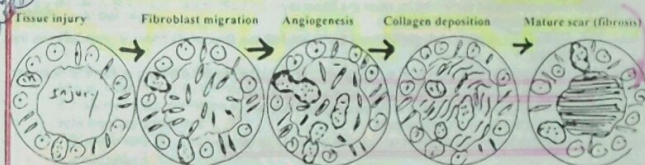
DEFINITION

Replacement of damaged tissue by granulation tissue which matures into fibrous (scar) tissue

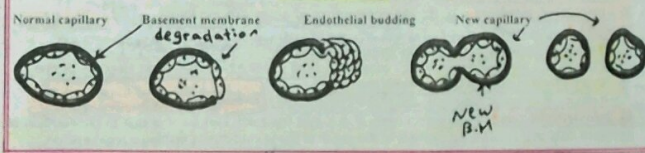
MECHANISM OF FIBROSIS

- The process starts by formation of granulation tissue (fibroblasts & capillaries), which matures into fibrous tissue by deposition of collagens followed by remodeling.
- The process is controlled by growth factors.
- Granulation** tissue appears moist, red (richly vascularized) and granular, while fibrous tissue is firm & grayish (hypovascular).
- The process of granulation tissue followed by fibrosis runs along the following steps:
 - Angiogenesis** (neovascularization): Formation of new capillaries occurs as follows:
 - Proteolytic degradation of the basement membrane of the parent vessel to allow for migration of endothelial cells, which proliferate forming solid endothelial buds.
 - Canalization (maturation) of endothelial buds to form capillary tubes which anastomose with adjacent.
 - Fibroblast migration, proliferation & secretion of collagen** (Fibrogenesis, fibrosis):
 - Migration of fibroblasts to the site of injury followed by fibroblast proliferation.
 - Fibroblasts secrete ECM proteins (fibronectin & proteoglycan) followed by type III collagen (thin fibrils) and later type I collagen (thick fibrils).
 - Progressive maturation & remodeling** to form the permanent scar (fibrous tissue):
 - Progressive type I collagen synthesis is accompanied by resorption of many capillaries by macrophages.
 - When the scar is big (in case of secondary union), some fibroblasts acquire a smooth muscle contractile function to minimize the scar size. These cells are called myofibroblasts.
 - Collagenases secreted by macrophages also modify the scar size. The mature (final) scar consists of matrix dense collagen (type I), few or no capillaries and inactive looking fibroblasts (resting fibrocytes). The scar is nearly avascular.

GRANULATION TISSUE



ANGIOGENESIS



③ examples

EXAMPLES OF HEALING BY FIBROSIS

1- HEALING OF WOUNDS

Wound
ep. dermis + dermis

Types Of Wound Healing

1) Healing by primary union (healing by first intention)

Wound characteristics: Non-gaping, clean (not infected) wound with minimal tissue loss & close edges. Best example is slitted surgical wound.

Mechanism of healing:

- After injury, the wound contains clotted blood and products of traumatic inflammation (neutrophils & macrophages). The surface of the wound is covered by dried clot (scab), which separates within 2 weeks.
- Phagocytosis of clot & products of injury & release of growth factors by macrophages.
- Epidermal cells (being labile) regenerate rapidly, starting from the basal layer at both sides of the wound, which meet at edge (since the wound is not gaping) & continue proliferation to restore the full epidermal thickness.
- Granulation tissue from the wound edges fills the gap under the epidermis.
- Maturation of granulation tissue into fibrous (scar) tissue.
- Skin adnexa (hair follicles, sweat glands, ...) lost within the wound will not regenerate.

2) Healing by secondary union (healing by second intention)

Wound characteristics: Gaping & infected wounds (including abscess ulcer, fistula, etc). There is marked tissue loss & edges are widely separated.

Mechanism of healing:

Mechanism of healing is basically the same as primary union with the following differences:

- Longer healing time
- Larger amount of granulation tissue → bigger scar.
- Epidermal regeneration is delayed than in primary union (see below).
- Wound contraction occurs in secondary union & constitutes another major difference.

Healing steps include:

- The wound is filled with clotted blood, debris, neutrophils, pus cells & macrophages.
- Phagocytosis & release of growth factors is done by macrophages.
- Epidermal cells start proliferation from the basal layer on both sides, but fail to meet (since the wound is gaping).
- Granulation tissue (describe) grows from the wound edges & wound bottom & gradually fills the wound gap.
- Epidermal regeneration can now successfully occur, since the proliferating epidermal cells can move on the surface of granulation tissue until they meet.
- Maturation of granulation tissue into fibrous (scar) tissue.
- Wound contraction by myofibroblasts.
- Skin adnexa within the wound are lost and do not regenerate.

Complications of Wound Healing

More common in secondary union

- Cosmetic deformities** due to extensive scarring.
- Functional troubles** e.g. due to contracture of scars around joints.
- Keloid:** *complication of wound healing* - It is a protuberant scar covered by stretched epidermis. It is due to overdone repair, which occurs in some susceptible persons as Negroes or due to presence of foreign bodies within the wound. It recovers after surgical excision but shrinks by irradiation.
- Epidermoid cyst** (implantation cyst): It is a cyst filled with keratin. It is due to proliferation of epithelial cells that may be trapped within the depth of the wound during epithelial regeneration.

Cosmetic ⇒ عيب
Cosmetic ⇒ عيب

Give an account Serofibrinous Inflammation?
Describe how does this lesion heal?

fibrosis
Mechanism
العملية

5) Chronic ulcer, chronic fistula or chronic sinus

Definitions:

- Chronic ulcer:** Persistent surface discontinuity due to loss of epithelium.
- Chronic Sinus:** A persistent blind-ended tract, opening to a surface by a single orifice.
- Chronic fistula:** A persistent double ended tract with openings on 2 surfaces.

Mechanism: Chronic ulcer, sinus & fistula are due to defective repair.

- This may be due to persistent infection → destruction of granulation tissue.
- It may be also due to excessive deposition of collagen at the edges of the wound without filling the whole wound with granulation tissue.

6) Carcinoma

may rarely develop from the epithelium related to a scar, particularly scars of burns. This type of squamous cell carcinoma is known as **Morjolin's ulcer**.

سرطانى

A comparison between the types of wound healing

A) Healing by Primary Union (First Intention)	B) Healing by Secondary Union (Second Intention)
Type of wound: clean, non-gaping e.g. surgical incision Mechanism of healing: Day 1: The narrow wound gap is filled with clotted blood and covered by a scab of dry clotted blood. Day 2: Epidermal regeneration occurs at both edges starting from the basal layer (accompanied by laying down of new basement membrane). The process is complete within 1-2 days. Exudation of neutrophils appears in the wound gap. Day 3: Macrophages replace neutrophils and start phagocytosis & secretion of growth factors. Day 4-5: Granulation tissue arises from the wound edges & fills the gap. Collagen fibrils start to appear. Second to fourth week: - The surface scab separates (by the end of the 2nd week). - Maturation of granulation tissue into fibrous tissue (describe). Finally the wound consists of a small mature scar covered by regenerated epidermis. - Skin adnexa do not regenerate. Complications: Less common	Type of wound: gaping, infected Mechanism of healing: Healing is basically similar to first intention, but differs in: Necrotic debris, clots & inflammatory cells (neutrophils & macrophages) are more extensive. Pus may also exist. Phagocytosis takes longer time & therefore the process of healing takes a longer period. - Epidermal proliferation starts early, but fails to reconstitute the epidermal covering, except after filling the gap with granulation tissue (which arises from edges & bottom & gradually fills the gap). By this time the epidermal cells can grow over the surface of granulation tissue to complete the process of epidermal regeneration. - The amount of granulation tissue is much larger, and consequently the scar is big. Wound contraction is a major difference, an action done by myofibroblasts. The wound finally consists of a contracted scar covered by regenerated epidermis without adnexa which do not regenerate. Complications: More common.

2-HEALING OF SEROFIBRINOUS INFLAMMATION ★

Mechanism: Fibrous healing of inflamed serous membranes occurs along the following steps:

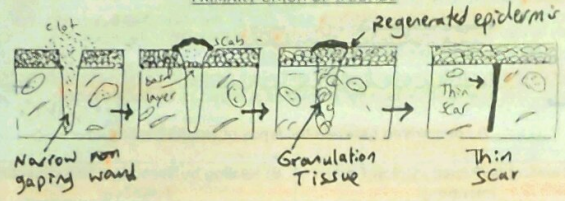
- The process starts by absorption of fluid exudate & phagocytosis of fibrin and debris
 - This is followed by granulation tissue (describe) derived from the subserosal tissue
 - Serosal cells regenerate.
 - Maturation of granulation tissue into fibrous tissue occurs.
- Complication:** Fibrosis may be extensive leading to fibrous extensions between visceral and parietal layers called adhesions. These adhesions may cause serious effects e.g. intestinal obstruction in case of peritoneal adhesions.

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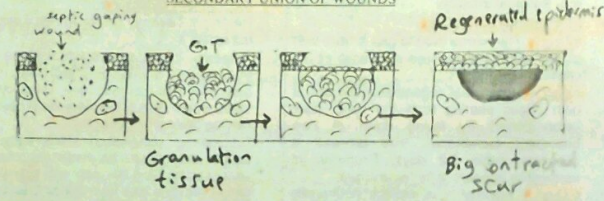
3-OTHER EXAMPLES OF FIBROSIS

- a) Fibrous organization of thrombi
- b) Infarcts
- c) Meningitis
- d) Arthritis (leading to ankylosis)
- e) Salpingitis (leading to tubal adhesions)
- f) Fibrous healing of bone in suboptimal conditions

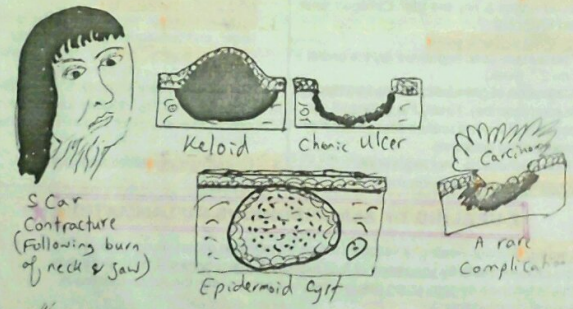
PRIMARY UNION OF WOUNDS



SECONDARY UNION OF WOUNDS



COMPLICATIONS OF WOUND HEALING



STEM CELLS

DEFINITION & SIGNIFICANCE OF STEM CELLS

- Stem cells exist in various parts of the human body at every stage of development from embryo to adult.
- They are the master cells of the human body. They are unspecialized cells that can divide giving copies of themselves, and under proper conditions can also develop into mature cells of different types such as liver cells, nerve cells, skin, pancreatic insulin producing cells, cardiac muscle, vessels and many others.
- Therefore, it is hoped that the recent exhaustive researches about stem cells could succeed to use these cells in repairing, treating and curing a variety of diseases & injuries. Examples of the potential therapeutic applications of these cells include:
 1. Generation of different types of neurons for the treatment of Alzheimer's disease,
 2. spinal cord injuries, or Parkinson's disease.
 3. Production of heart muscle cells to repair myocardial injury.
 4. Generation of insulin-secreting pancreatic islet cells to treat type-1 diabetes.
 5. Generation of hair follicle stem cells for the treatment of certain types of baldness.
 6. Production of complete organs as livers, kidneys, eyes, hearts, or even parts of brain.
 7. Drug testing.
 8. Cancer research.
 9. Research on embryonic development.

TYPES OF STEM CELLS:

- A) **Totipotent cells.** In mammals, totipotent cells have the potential to become :
 - Any type in the adult body;
 - Any cell of the extra-embryonic membranes (e.g., placenta).
 - The only totipotent cells are the fertilized egg (zygote) and the first few primitive cells produced by its division
 - In mammals, the expression totipotent stem cells is a misnomer, since totipotent cells cannot make more of themselves.
- B) **Pluripotent stem cells.** These are true stem cells, which can only be isolated from embryonic or fetal tissue.
 - They can be grown in specific cultures to reproduce themselves without differentiation
 - They can also –be special measures - make any differentiated cell in the body.
 - Three types of pluripotent stem cells have been found

1-Embryonic Stem (ES) Cells.

These cells are isolated from the inner cell mass (ICM) of the blastocyst which is found in an early phase of embryonic development. For human research and treatment purposes, these cells can be obtained from excess embryos produced during in vitro fertilization (IVF).

Remarks about IVF:

- The process of IVF includes drug (hormone) stimulation of ovulation in the committed female → numerous ova are produced in her ovaries. The ova are then surgically extracted from her ovaries.
- Meanwhile, sperms are extracted from the testis of the committed male (who often suffers from obstructive azoospermia i.e. he has sperms in his testis without passing in his ejaculate due to pathway obstruction).

White Knight Lane

- Thereafter, sperms are injected into the ova i.e. in vitro fertilization (IVF) → many embryos.
- Two or three of these embryos are then implanted in the uterus of the female, while the rest of embryos are kept frozen. If pregnancy successfully continues in the committed female followed by delivery of an alive baby (or babies), the frozen embryos may be discarded. These discarded embryos can be used as a source of ES cells. However, there is still much discussions about the ethical aspect of using embryos as a source of EC cells

2-Embryonic Germ (EG) Cells

These can be isolated from the precursor gonadal cells of aborted fetuses.

3-Embryonic Carcinoma (EC) Cells. These can be isolated from teratocarcinoma (a special tumor that occasionally occurs in a gonad of a fetus). Unlike the other two, these cells are usually aneuploid. *no of chromosome isn't exact no. multiple of 23*

C) Multipotent stem cells

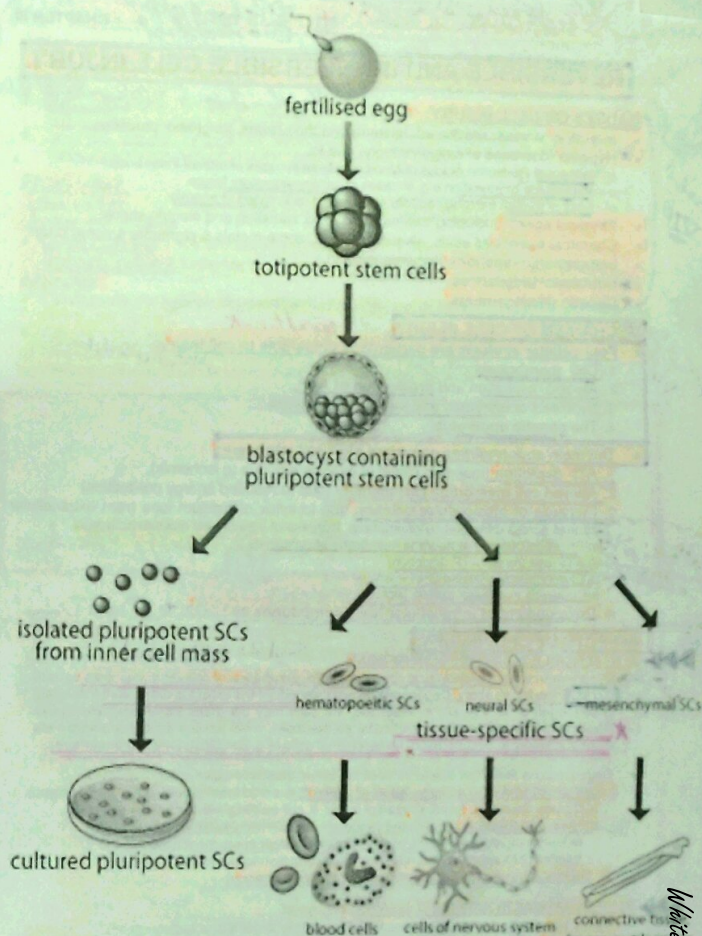
- These are true stem cells but can only differentiate into a limited number of types. For example, the bone marrow contains multipotent stem cells that give rise to all the cells of the blood but not to other types of cells.
- Multipotent stem cells are found in adult animals; perhaps most organs in the body (e.g. bone marrow, brain, liver, gut...) contain them, where they can replace dead or damaged cells. These adult stem cells may also be the cells that can give rise to a clone of cancer cells if they accumulate sufficient mutations.
- Like embryonic stem cells, these adult stem cells can make identical copies of themselves for long periods of time (self-renewal).
- At the same time, they can give rise to mature cell types that have characteristic shapes and specialized functions.
- Stem cells typically generate an intermediate cell type (s) before they achieve their fully differentiated state. The intermediate cell is called a progenitor cell. Progenitor cells are partly differentiated cells in the sense that they are committed to a particular cell lineage and, upon division, and give rise to differentiated cells.
- Hematopoietic stem cells (HSCs) are the best characterized adult stem cells.

STEM CELL PLASTICITY

- Adult stem cells were believed to be irreversibly committed to specific lineages of differentiation without capability to give rise to other tissues, e.g. bone marrow HSCs which normally give rise to all types of blood cells.
- However, a number of recent experiments over the last several years have raised the possibility that stem cells from one tissue may be able to give rise to cell types of a completely different tissue. This phenomenon is known as 'stem cell plasticity'.
- Examples of such plasticity include bone marrow stem cells becoming neurons, or pancreatic islet cells that are capable of producing insulin.

SOURCES OF STEM CELLS

- Aborted fetuses or fertilized eggs (IVF embryos): ethical considerations limit their utility
- Bone marrow, peripheral blood or umbilical cord blood: These sources for stem cells are ethical and legal. Adult stem cells are obtained and engineered to give rise to any adult tissue in the body.
- Skin, pulp of milk teeth, fat cells are recent sources of adult stem cells



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REVERSIBLE AND IRREVERSIBLE CELL INJURY

CAUSES OF CELL INJURY:

- Infection: viruses, rickettsiae, bacteria and their toxins, fungi and parasites.
- **Hypoxia** (decrease of oxygen supply) due to:
 - Ischemia: Reduction or loss of blood supply as in cases of arterial thrombosis.
 - Inadequate oxygenation e.g. in cases of cardio-respiratory failure.
 - Loss of oxygen carrying capacity of the blood as in cases of anemia.
- Physical agents including trauma, heat, cold, radiation and electric shock.
- Chemical agents as acids, alkalies, alcohol, some metals & pigments & some drugs.
- Immunologic reactions (hypersensitivity).
- **Nutritional imbalances.**
- **Genetic derangements.**

MECHANISM OF CELL INJURY

- Four cellular systems are particularly vulnerable to cell injury:
 1. Cell membranes
 2. Aerobic respiration and production of ATP
 3. Synthesis of enzymes and structural proteins.
 4. The genetic apparatus
- The main abnormalities occurring after cell injury are:
 1. ATP depletion (mainly in cases of hypoxia e.g. due to ischemia).
 2. Altered cell membrane permeability (due to reduced energy production)
 3. Increase of intracellular calcium due to influx of calcium ions from extracellular spaces across damaged cell membrane. Increase of intracellular calcium activates:
 - a) Phospholipases that degrade membrane phospholipids.
 - b) ATP-ase (cause ATP depletion)
 - c) Endonucleases (cause DNA injury)
 - d) Proteases that break cellular proteins
 4. Development of intracellular toxic compounds as H_2O_2 + DNA Damage

EFFECTS OF CELL INJURY:

A) REVERSIBLE INJURY (DEGENERATION):

- Degenerations are morphological changes due to disturbance of cellular metabolism caused by mild (non-lethal) injury. Degenerations are reversible if the irritant is removed. If the irritant is prolonged or its intensity is increased, the cells may die (necrosis) irreversible injury.
- Parenchymal (metabolically active) cells, as liver cells, renal tubules & cardiac muscle are more vulnerable to degeneration. Mesenchymal cells (e.g. fibroblasts) are more resistant.
- Degenerations are either due to intracellular accumulation of water or fat:
 1. Cell swelling due to accumulation of water. It is a mild form of cell injury. Two subtypes:
 - a) Cloudy Swelling: Small amount of water → cell swelling with granular cytoplasm
 - b) Hydropic Swelling (also called vacuolar degeneration, hydropic degeneration or ballooning degeneration). Accumulation of larger amounts of water → the swollen cells appear pale and show clear cytoplasmic vacuoles
 2. Cell swelling due to accumulation of fat (Fatty change)

B) IRREVERSIBLE INJURY (CELL DEATH):

- Two types:
 1. **Necrosis:** due to severe or prolonged cell injury (same causes of degeneration).
 2. **Apoptosis:** This is cell suicide (programmed cell death). It occurs in certain circumstances, frequently unrelated to tissue irritation

Reversible cell injury

CELL SWELLING DUE TO ACCUMULATION OF WATER

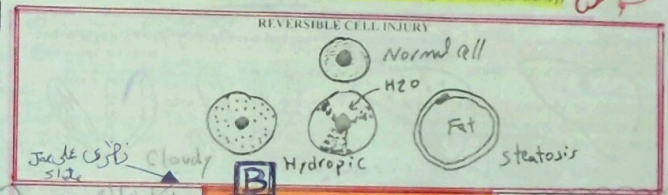
PATHOGENESIS: Define: Mild injury (particularly mild hypoxia) → inhibit oxidative phosphorylation → suppression of ATP production → leads to:

- Disruption of membrane transport mechanisms → sodium enters the cell (due to water) & potassium diffuses out of the cell → cell swelling
- Impaired cellular metabolism → accumulation of metabolic products: lactate & pyruvate
- Consequently increased intracellular osmotic load → cell swelling

 Note: ATP = Adenosine Triphosphate

PATHOLOGY

- **Gross picture:** The affected tissue or organ appears swollen and pale.
- **Microscopic picture:**
 - **Cloudy swelling:** Cells are swollen showing pale eosinophilic granular cytoplasm & faint vacuolation.
 - **Hydropic swelling:** Cells are swollen with a single large clear vacuole or multiple vacuoles.
- **Examples:**
 - Cloudy swelling or hydropic degeneration (ballooning) of renal tubules in cases of nephritis & liver cells in viral hepatitis.
 - Ballooning of B cells of islets of Langerhans in cases of diabetes mellitus.
 - Ballooning of epidermal cells in cases of viral infections & mild burns.
 - Ballooning of renal tubule in cases of electrolyte imbalance (potassium deficiency).



FATTY CHANGE (STEATOSIS)

DEFINITION: Accumulation of lipids (neutral fat) inside parenchymal cells. It can affect the heart, kidney & other organs, but is by far most common in the liver (hepatic steatosis).

AETIOLOGY: CAUSES & PATHOGENESIS

1. **Fatty change of liver:** Causes (6 pathogenesis) include:
 - a) **Hypoxia or bacterial toxins** → suppression of mitochondrial lipid metabolism enzymes → intracellular accumulation of fat
 - b) **Hepatocellular specific causes:** Since the liver is the main organ responsible for fat metabolism, its cells may undergo fatty change in the following conditions:
 - **Excess fat** carried to liver cells (more than their capacity to utilize these amounts) e.g. Obesity (excess dietary fat) → due to lipogenesis
 - **Starvation & diabetes mellitus** → excessive mobilization of fat from fat stores to liver
 - **Deficiency of lipotropic factors** as choline & methionine → accumulation of neutral fat inside liver cells
 - **Hepatotoxins** as alcohol which → fatty acid synthesis & fatty acid oxidation
 - **Peripheral lipolysis:** There are many other hepatotoxins as CCl₄ & some drugs
 - **Some liver cell diseases** as viral hepatitis C
2. **Fatty change of other organs** (as kidney & heart) is mainly due to hypoxic or toxic damage of mitochondrial enzymes

Write tonight alone

* Special stain for fat

PATHOLOGY:

Gross Picture:

The organ appears enlarged with tense capsule. Consistency is soft greasy. Cut surface is bulging & borders are rounded. Color is yellow, diffuse or patchy.

The most commonly affected organs are

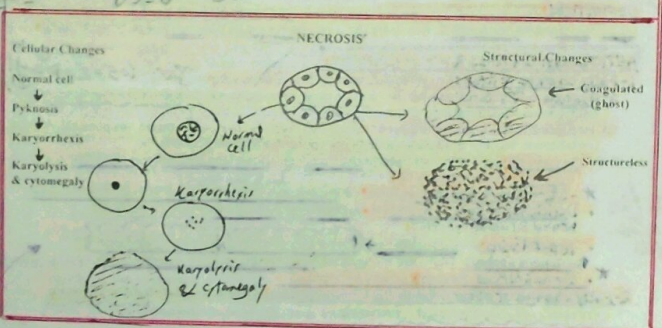
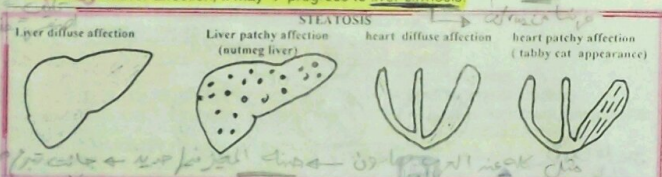
- 1-Liver:** Affection may be extensive (diffuse) as in severe toxic injury or potty (patchy) due to milder injury as hypoxia. In such cases the liver appears mottled (nutmeg appearance).
- 2-Heart:** Affection may be also diffuse as in cases of diphenhelic toxic myocarditis or patchy such as in hypoxic cases. Patchy affection of the myocardial fibers → yellow streaks alternating with the non-affected brownish muscle fibers → tigroid or tabby cat appearance.
- 3-Kidney:** Affection is mainly cortical (where tubules exist) & is spotty or rarely diffuse.

Microscopic Picture

- With ordinary stains fat appears as small clear fat vacuoles or a single large vacuole that may flatten the nucleus and displace it eccentrically → signet ring appearance.
- With special stains, fat can be stained orange (Sudan III) or black (osmic acid).

Clinical Significance

- Fatty change is a severer form of cell injury that may progress to cell necrosis resulting in:
- In case of diffuse heart affection it may → heart failure
- In case of liver affection, it may → progress to liver cirrhosis.



irreversible cell injury

APoptosis @ Necrosis

Not autolysis in dead body

DEFINITION: Necrosis means death of a group of cells within a living body caused by an irritant.

CAUSES & PATHOGENESIS: See before (causes & pathogenesis of reversible & irreversible cell injury).

GROSS FEATURES:

- The necrotic tissue appears opaque yellow and may be swollen.
- The surrounding tissues appear hyperemic due to inflammation.

MICROSCOPIC FEATURES:

1-Cellular Changes:

- a) Nuclear Changes:** Due to enzymatic digestion.
 - Pyknosis: The nucleus becomes small and dark.
 - Karyorrhexis: Nuclear fragmentation.
 - Karyolysis: Faint dissolved nucleus.

b) Cytoplasmic Changes:

- The cells may appear swollen (cytomegaly).
- Cell membranes appear indistinct.
- Cytoplasm is eosinophilic (staining of denatured proteins).

2-Architectural Changes: Two main possibilities. = structureless

- a) Necrotic tissue may rapidly appear structureless** due to cell lysis (autolysis by lysosomal enzymes of the dead cells + heterolysis by proteolytic enzymes derived from inflammatory cells in the area).
- b) Protein denaturation (coagulation)** may precede cell lysis (mainly in cases of ischemia). In such cases the necrotic cells preserve the architectural outlines of the original tissue → structural ghost. However lysis occurs later and the necrotic tissue finally appears structureless.

FATE OF NECROTIC TISSUE:

- Inflammation surrounds the necrotic area due to release of chemical mediators.
- Healing: Regeneration or fibrosis (depending on type of damaged cells).
- Dystrophic calcification may occur.

TYPES OF NECROSIS:

1-Coagulative Necrosis:

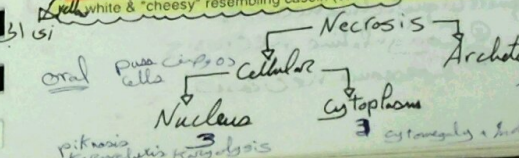
- It occurs in infarcts (ischemic necrosis) of all organs except CNS.
- There is denaturation of cell proteins, which lasts for at least some days; thus the basic outline of the necrotic cell is preserved despite loss of the nuclei. Finally lysis occurs and the necrotic tissue becomes structureless.

2-Liquefactive Necrosis:

- Occurs in infarcts of CNS (unknown reasons) and in pus.
- It is due to prevalence of cell lysis over protein denaturation as in case of pus (by proteolytic enzymes liberated from pus cells) (see mechanism of pus formation).

3-Gangrenous Necrosis: This necrosis (usually coagulative or liquefactive) followed by putrefaction by saprophytes.

4-Caseous Necrosis: This type of necrosis is typical of tuberculosis. The necrotic tissue appears yellowish white & "cheesy" resembling casein (caseous). The caseous appearance is explained by



glia in brain but no fibrosis in brain the difference in conductivity when all die & small

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Coagulative → liquefactive → caseous → fat necrosis → fibrinoid

Coagulative → liquefactive → caseous → fat necrosis → fibrinoid

Necrosis starts as ischemic coagulative necrosis due to endarteritis obliterans
 Coexisting hypersensitivity (allergic inflammation) due to tuberculous antigens (tuberculo-protein) → release of cytotoxins and proteolytic enzymes → partial liquefaction of the coagulated necrotic cells → cell fragmentation
 Tubercle bacilli are rich in fats. Liberation of these fats from dead bacteria adds to the cheesy character of this type of necrosis.

Microscopically, it appears granular eosinophilic structureless material (fragmented necrotic cells). slide 23 **Ranogamous pink structureless = Caseation**

Fat Necrosis: Two subtypes:

a) Enzymatic Fat Necrosis:

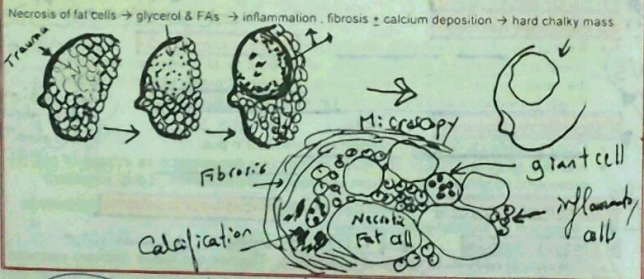
- Cause:** It occurs in cases of acute hemorrhagic pancreatitis
- Mechanism:** Ruptured pancreatic ducts → escape of lipase and protease enzymes → digestion (necrosis) of the surrounding peritoneal fat cells
- Grossly:** The affected areas may show chalky white hard calcific patches. This is because fatty acids liberated from necrotic fat cells have a high affinity to combine with calcium forming calcium soaps.
- Microscopically:** Swollen necrotic fat cells, surrounded by chronic inflammatory cells (including foreign body giant cells) and fibrosis, sometimes with calcification.

b) Traumatic Fat Necrosis:

- Cause:** It is common in the female breast and subcutaneous fat & is usually caused by trauma (which may be surgical)
- Mechanism:** Rupture of fat cells results in their auto-digestion and release of fatty acids, which combine with calcium
- Grossly:** Hard, sometimes chalky white mass. It may be clinically mistaken for a tumor as in case of fat necrosis of the breast. Biopsy will diagnose the condition
- Microscopically:** resembles enzymatic fat necrosis (describe).

Fibrinoid Necrosis: It affects muscle fibers & collagen which become fragmented → finer particles resembling fibrin. It develops in autoimmune collagen diseases (as rheumatic fever, rheumatoid arthritis, lupus erythematosus, etc). It is due to autoantibodies against collagen. It is not true necrosis since it does not affect living cells.

TRAUMATIC FAT NECROSIS



Irreversible cell injury

Necrosis	Apoptosis
Inflammation	not

APOPTOSIS Programmed cell death

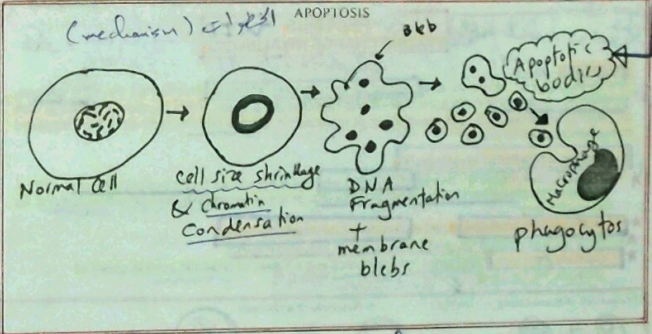
DEFINITION: Apoptosis in Greek means 'dropping off'. It is another form of cell death that usually involves few or single cells. This type of cell death seems to be programmed and is described as cell suicide or programmed cell death aiming at removal of un-necessary or (diseased) cells. It can occur in physiological & pathological conditions. It can occur without tissue injury (or with mild injury not causing necrosis). Apoptosis is not associated with release of chemical mediators & therefore does not excite inflammation.

MORPHOLOGICAL FEATURES OF APOPTOSIS

- Shrinkage of cell size
- Nuclear chromatin condensation, followed by fragmentation of DNA
- Formation of membrane blebs, followed by their separation → apoptotic bodies
- The apoptotic bodies consist of a dark nuclear fragment surrounded by eosinophilic cytoplasm. They become engulfed by phagocytic cells
- Apoptosis does not excite inflammation & is not accompanied by healing or calcification.

EXAMPLES OF APOPTOSIS: Occurrence of apoptosis is known in several conditions:

- In physiological (normal) states** such as:
 - During embryogenesis in 3rd month
 - Hormone dependent involution of tissues e.g. endometrium during menstrual cycle
 - Cells after achieving their purpose e.g. neutrophils in acute inflammation
 - Normal turn over of cells (e.g. intestinal epithelium) to maintain a constant number of cells.
- In pathological states** such as:
 - Liver cells in viral hepatitis (Councilman bodies)
 - Apoptosis of malignant tumor cells
 - In some cases of atrophy
 - In cases of mild radiation injury and mild thermal injury
 - Cytotoxicity induced by T lymphocytes as in organ rejection



1. Define Councilman bodies

- Define Liquefactive necrosis
- Coagulative necrosis
- Caseous necrosis

Write tonight alone

نوع الروب غني ولا ينجب مع نفسه

CHAPTER IV

INTRACELLULAR ACCUMULATIONS AND EXTRACELLULAR DEPOSITIONS

1- INTRACELLULAR ACCUMULATIONS

1 WATER

See cloudy swelling & hydropic degeneration

2 FATS

- Fatty change: See before
- Atherosclerosis: See systemic pathology
- Xanthoma: Deposition of fat in skin (engulfed by dermal macrophages)
- Gaucher's disease: Accumulation of glucocerebrosides inside phagocytic cells.
- Neimann Pick's disease: Accumulation of sphingomyelins inside phagocytic & parenchymal cells

3 MUCIN MUCOID DEGENERATION

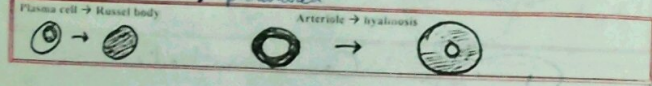
- This is accumulation of mucin inside epithelial cells which swell & show vacuolated cytoplasm, may be with eccentric nuclei (signet ring cells). Cells may rupture leading to extracellular pools of mucin.
- Occurs in a number of pathological conditions. Examples
 - In case of catarrhal inflammation (see before)
 - In case of mucoid and signet ring cell carcinoma (see later)
 - In case of mucinous cystadenoma of the ovary (see later)
- Remark: Extracellular accumulation of mucin is called Myxomatous Degeneration (see later)

4 PROTEINS HYALINE CHANGE (HYALINOSIS)

Definition: The term "hyaline" refers to any cellular or extracellular alteration manifested by homogenous, glassy-pink appearance in sections stained with hematoxylin & eosin. It is a microscopic change with no specific gross features. The mechanism of hyalinos is excess protein, synthesized or deposited in the affected cell or matrix.

Examples of Cellular Hyalinos

- Russell bodies: Hyaline change of plasma cells which appear as bright eosinophilic oval bodies. It is due to overproduction of immunoglobulins in some prolonged chronic inflammations as rheumatoid arthritis.
- Mallory alcohol hyaline: seen in liver cells in alcoholic hepatitis.
- Hyaline inclusions of Langerhans in cases of diabetes mellitus.
- Corpora amylacea: Laminated hyaline bodies in the lumen of prostatic acini in cases of prostatic hyperplasia & prostatic carcinoma.



Complete lat. Mallory bodies

- ② Councilman bodies
- ③ Russell bodies

وجود من السحابة تاليف هذا هو ان الحبيب الذي لا يموت (منه)

Examples of Extracellular (Connective Tissue) Hyalinos:

- Hyalinos of old scars and keloids.
- Hyalinos of organized (fibrotic) thrombi.
- Hyalinos of some mesenchymal tumors as leiomyoma.
- Vascular Hyalinos: Examples
 - Hyalinos of arteriolar walls in cases of hypertension diabetes mellitus & old age
 - Hyalinos of fibrosed glomeruli in cases of chronic glomerulonephritis

6 GLYCOGEN

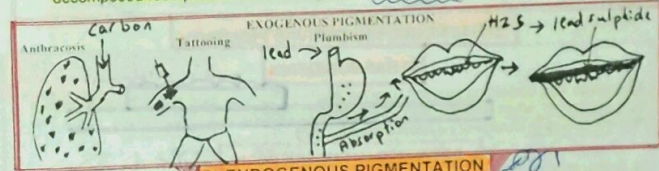
In case of glycogen storage diseases

6 PIGMENTS

Intracellular accumulation of pigments includes two major forms:

A) EXOGENOUS PIGMENTATION

- By inhalation:** The most common example is anthracosis which is black pigmentation of lungs caused by inhalation of carbon due to smoking or air pollution. This carbon is engulfed by macrophages and is partly carried to the draining lymph nodes.
- By skin inoculation (tattooing):**
- By ingestion:** In cases of chronic lead poisoning (plumbism) there is blue black pigmentation of the gums due to combination of lead with hydrogen sulphide (from decomposed food particles between teeth) → lead sulphide.



B) ENDOGENOUS PIGMENTATION

1-MELANIN

Melanin is formed by melanocytes from tyrosine by action of tyrosinase. It normally exists in skin, hair, eyes, meninges and basal ganglia.

Causes of increased melanin pigmentation (Hyperpigmentation):

- Prolonged exposure to sun
- Addison's disease: Chronic adrenocortical insufficiency → feed back → rise of ACTH (which has a melanocyte hormone like action) → Pigmentation of skin & mucous membranes
- Pigmented tumors: Benign melanoma (nevus) and malignant melanoma
- Melasma (Chloasma): Hyperpigmented melanotic patches affecting face of women during pregnancy (associated with pigmentation of nipples and genitalia)
- Cafe au lait skin patches in patients with multiple neurofibromatosis

Causes of deficient melanin pigmentation (Hypopigmentation):

- Albinism: This is generalized hypopigmentation due to tyrosinase deficiency. It is an inherited autosomal recessive defect characterized by absence of melanin pigment in hair, skin & iris & choroid of eyes
- leukoderma: Patchy skin hypopigmentation. May be congenital or acquired (as in leprosy)

Agnes de plumbism

* How the pigment Lipo-fuscin appears?
 في اليوسيفوسين
 2- LIPOFUSCIN (LIPOCHROME)
 Jar +

This yellowish brown lipid-derived pigment normally exists in small amounts in different cells of the body. Pigment is increased most commonly in cases of organ atrophy. Example:

1) **Brown Atrophy Of The Heart:** Jar * C18-1 - Brown atrophy of heart + atrophy of cells
 Cause: Generalized atrophy in old age (senile atrophy) or wasting diseases.
 Pathogenesis: Lipo-fuscin is normally derived from peroxidation of polyunsaturated lipids of cellular membranes. This process is exaggerated in atrophic cells. Since aging (senility) is the commonest cause of atrophy, lipo-fuscin is sometimes considered as a wear-and-tear or aging pigment. Therefore organ atrophy may be accompanied by dark brown coloration (brown atrophy).
 Gross Features: Heart is reduced in size & has dark brown myocardium. Coronaries appear tortuous & pericardial fat disappears. Jar in pericardial
 Microscopic Features: Brownish lipo-fuscin granules are seen in atrophic muscle fibers.

2) **Melanosis Coli:** This is brown black lipo-fuscin pigmentation of colonic mucosa occurring in patients with habitual intake of anthraquinone purgatives. Increased lysosomal activity of intestinal macrophages from which this pigment is derived.



3- HAEMOGLOBIN-DERIVED PIGMENTS

1) HAEMOSIDERIN

A brownish iron containing pigment. It gives positive Prussian blue reaction i.e. it gives a blue coloration when treated with potassium ferrocyanide & hydrochloric acid. The pigment occurs in localized or systemic forms.

LOCALIZED HAEMOSIDEROSIS

In areas of hemorrhage, haemosiderin appears inside & outside macrophages. The affected tissue appears brownish & firm due to fibrosis. Examples: in cases of lung congestion and endometriosis.

GENERALIZED HAEMOSIDEROSIS (HEMOCHROMATOSIS)

Pathogenesis of hemochromatosis: excess accumulation of body iron:
 Normally iron is absorbed from the intestine → blood → carried & stored inside the cells in association with a protein called apoferritin forming together ferritin micelles
 If there is abnormal iron overload → excess ferritin micelles which aggregate → hemosiderin → abnormal brown pigmentation of the affected cells.
 Hemosiderin accumulates both in parenchymal cells and phagocytic cells (mononuclear phagocytes, reticuloendothelial cells).
 In primary hemochromatosis there is a genetic error leading to excess absorption of dietary iron → prolonged iron overload (for years) → progressive damage of the affected parenchymal cells → serious effects (see below).
 In secondary hemochromatosis, iron overload may be transient as in cases of repeated blood transfusions → mild transient parenchymal cell affection → less marked damage. However significant affection may occur in some of the secondary type such as iron overload due to chronic bone marrow hypofunction → impaired iron utilization → prolonged increase of blood iron.

Types of hemochromatosis

a- Primary Haemochromatosis (Bronzed Diabetes)

Aetiology: Iron overload due to an inborn error characterized by increased absorption of dietary iron. It is also called hereditary hemochromatosis (HHC). It mainly affects males and is rare in females (due to physiological loss of iron in menses and pregnancy). Iron accumulation is lifelong and around the 5th decade it will be severe enough to cause symptoms and complications.

Pathology & Effects: Plasma iron level is elevated. The parenchymal cells (and phagocytes) show hemosiderin deposits. Progressive parenchymal damage → cell necrosis and fibrosis. The affected organ is enlarged, brown & firm. The main manifestations of primary hemochromatosis are:

- 1- Skin: Bronzed coloration due to hemosiderin deposits & 2ry increase of melanin
- 2- Diabetes mellitus due to pancreatic destruction. The pancreas is brownish & firm
- 3- Pigmentary cirrhosis due to liver destruction. Liver is brownish, firm and nodular. Malignancy (hepatocellular carcinoma) complicates 10% of cases
- 4- Heart is enlarged, pigmented and shows fibrosis → Heart failure
- 5- Affection of other sites e.g. joints (synovitis), testis, endocrine glands, etc.

b- Secondary Hemochromatosis (Secondary Haemosiderosis)

Aetiology: Iron overload due to:

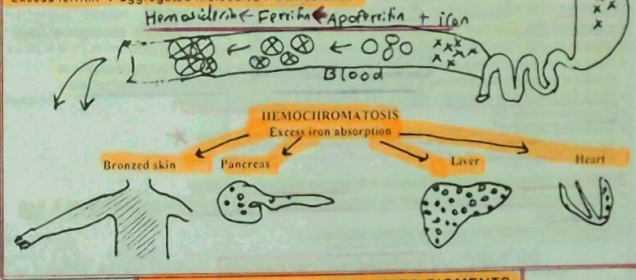
- 1- Repeated blood transfusions.
- 2- Hemolytic anaemias
- 3- Impaired utilization of iron as in cases of bone marrow hypofunction
- 4- Excess intake of iron e.g. with iron therapy → injection related not oral *

Pathology: Brown hemosiderin pigment appears in phagocytic cells & parenchymal cells e.g. of different body organs, but cellular damage is milder than in primary hemochromatosis.

FORMATION OF HAEMOSIDERIN

Blood iron + apoferritin → ferritin

Excess ferritin → aggregated molecules → hemosiderin



2) OTHER HEMOGLOBIN DERIVED PIGMENTS

- a) **BILIRUBIN** - An iron-free pigment. It is increased in cases of jaundice. It gives positive Prussian blue reaction.
- b) **HAEMATIN** - A brown pigment produced by action of acids or alkalis on hemoglobin (e.g. hematin which develops in the stomach in case of gastric hemorrhage).
- c) **HAEMOZOIN** - A brownish iron containing pigment related to hematin. It is produced by parasites feeding on blood cells as in cases of Bilharziasis & malaria. The pigment is released in blood → engulfed by macrophages of liver, spleen & other organs → macrophage pigmentation called parasitic pigmentation.

* Haematin & haemosiderin are both brown pigments.
 1st - haematin is produced by parasites feeding on blood.
 2nd - haemosiderin is produced by repeated blood transfusion.
 Oral

abnormal regulation of iron metabolism
 abnormal regulation of iron metabolism

أي مكان لها
العلم والأمراض
T.I.O

II- EXTRACELLULAR DEPOSITIONS

CALCIUM

PATHOLOGICAL CALCIFICATION

Definition: Deposition of calcium salts in sites other than bones and teeth
Grossly, the calcified tissue appears chalky white and hard
Microscopically, calcification appears as blue granules (with hematoxylin & eosin)
Types of pathological calcification include

1- DYSTROPHIC CALCIFICATION

Definition: This is calcification of dead or degenerated tissues in spite of a normal blood calcium level. It is the most common type of pathological calcification.

Pathogenesis: It is due to breakdown of organic phosphates $\rightarrow$ change of pH (alkalinity) of dead tissues and increased phosphatase activity $\rightarrow$ calcium deposition.

Examples: $\rightarrow$ cholesterol (soft) $\rightarrow$ 4Ca^{+} (Rural) = dystrophic calcification

- Atherosclerosis
- Goitre
- Degenerated tumors as leiomyoma & necrotic tumors as breast cancer
- Degenerated valves as in chronic Rheumatic valvulitis & in old age.
- Caseous tuberculous lesions
- Dead parasites and ova as bilharziasis
- Fat necrosis
- Thrombi, particularly venous thrombi (phlebotomy).
- Lithopedion (intrauterine dead calcified fetus)

2- METASTATIC CALCIFICATION

Definition: This is calcification of normal tissues due to hypercalcaemia.

Pathogenesis: Causes of hypercalcaemia include increased calcium absorption from intestine and/or increased calcium mobilization from bone as in cases of:

- Hyperparathyroidism including primary hyperparathyroidism (due parathyroid hyperplasia or functioning parathyroid tumors) & secondary hyperparathyroidism in case of chronic renal failure.
- Bone destruction by malignant tumors (as myeloma & metastatic cancer).
- Hypervitaminosis D
- Excessive intake of milk (rich in calcium) in patients with peptic ulcers.
- Systemic sarcoidosis $\rightarrow$ secretes parathormone like substance

Sites: Any tissue, but principally tissues with relative alkalinity including:

- Tissues that secrete acidic products as stomach mucosa, renal tubules (nephrocalcinosis) & lung alveolar walls.
- Arterial walls (which are normally slightly alkaline).

3- IDIOPATHIC CALCINOSIS

A rare type of calcification of unknown aetiology. It may be localized affecting a focus of skin & soft tissue $\rightarrow$ nodular masses of calcium (termed "tumoral calcinosis"). It is rarely generalized (calcinosis universalis) affecting skin, soft tissues & nerves.

4- STONES

Urinary stone, biliary stones & salivary duct stones: See systemic pathology.

DYSTROPHIC & METASTATIC CALCIFICATION

Dystrophic Calcification

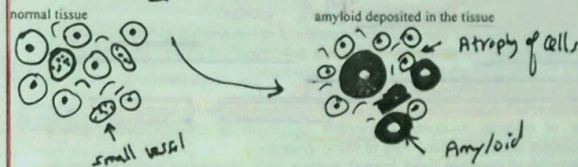
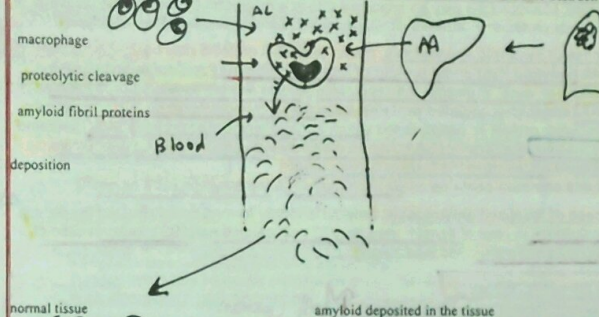


Metastatic Calcification



SYSTEMIC AMYLOIDOSIS

Plasma cell dyscrasia $\rightarrow$ AL $\leftarrow$ AA $\leftarrow$ liver reaction $\leftarrow$ Chronic destructive disease



Extracellular

AMYLOIDOSIS

DEFINITION: Protein

Amyloidosis (also called **β fibrilosis**) is extracellular deposition of amyloid substance, mainly in walls of blood vessels, basement membranes & along reticular fibers.

Although protein in nature, it was termed amyloid i.e. starch-like because it reacts with iodine and sulphuric acid giving a blue color.

STAINING OF AMYLOID:

- Gross Staining:** is done on slices of the suspected organ e.g. on post mortem specimens.
 - Lugol's iodine stains amyloid dark brown and the rest of tissue pale yellow.
 - Iodine and 1% sulphuric acid stain the amyloid blue.
- Microscopic staining:** Can be done on paraffin sections or frozen sections.
 - Hematoxylin & eosin stain: Amyloid appears homogenous & eosinophilic (pale red).
 - Congo red stain: Amyloid is stained **orange red**. If the same sections are examined under polarizing light, amyloid exhibits characteristic apple-green bipolar refringence.
 - Metachromatic stains as crystal violet or methyl violet stain the amyloid deposits rose red while the rest of tissues are stained violet.

DIAGNOSIS OF AMYLOIDOSIS DURING LIFE: Mostly generalized disease

By biopsy from suspected sites as kidney. In case of suspected generalized amyloidosis biopsies are easiest from rectum or gingiva. Microscopic examination of biopsy specimens aided by special stains (as Congo red) will diagnose the condition.

NATURE OF AMYLOID:

90% of the amyloid is a fibril protein & the remaining 10% is a glycoprotein called P component. Macrophages play an important role in amyloidosis by proteolytic cleavage of the precursor proteins → amyloid fibrils. Amyloid fibril proteins are of several types:

- In case of systemic amyloidosis,** the amyloid fibril proteins may be:
 - AL (amyloid light chain protein of immunoglobulins):** It is secreted by plasma cells in case of plasma cell neoplasms (known as plasmacytoma or myeloma).
 - AA (amyloid-associated protein):** It is a non-immunoglobulin protein present as a precursor protein in serum called serum amyloid associated protein (SAA) secreted by the liver. Synthesis of SAA may be markedly increased in chronic destructive disease anywhere in the body as tuberculosis.
 - Less common proteins** as B2 microglobulin & transthyretin (pre-albumin).
- In case of localized amyloidosis,** amyloid is locally formed in the affected tissue, e.g. procalcitonin in case of thyroid medullary (C cell) carcinoma, AB2 protein in case of cerebral amyloidosis... etc (see below).

TYPES OF AMYLOIDOSIS:

- Systemic (Generalized) Amyloidosis:** Most Common

Many organs are affected. Most common causes of death are: renal failure, heart failure, malabsorption (when bowel is affected) & Addison's disease (when adrenal glands are involved). Types of generalized amyloidosis:

 - B Cell Dyscrasias (Primary Amyloidosis):**
 - AL is secreted due to abnormalities of B lymphocytes and plasma cells as in cases of multiple myeloma (malignant neoplasm of plasma cells), where amyloidosis occurs in about 15% of these patients.
 - It affects heart (causing heart failure), tongue, GIT, skeletal muscles as well as other organs as kidney.

الخلايا لا ياتي لشاى المستأثر

b) Reactive Systemic Amyloidosis (Secondary Amyloidosis): AA Type

- AA is increased causing generalized amyloidosis in the following chronic severe destructive conditions:
 - Chronic suppurations: e.g. chronic osteomyelitis, chronic lung abscess, chronic empyema & bronchiectasis.
 - Granulomas as tuberculosis.
 - Autoimmune diseases as ulcerative colitis & rheumatoid arthritis.
 - Some malignant tumors as Hodgkin's disease & gastric carcinoma.
- It most commonly affects kidneys, liver, spleen & adrenal glands.

c) Hereditary Amyloidosis: Several types. The amyloid protein is AA or transthyretin (prealbumin). It may be generalized (as in familial Mediterranean fever) or localized.

2) Hemodialysis-associated Amyloidosis: Affects up to 70% of patients with chronic renal failure subjected to chronic hemodialysis. It is due to deposition of the amyloid protein "B2 microglobulin" which is not filtered by normal dialysis membranes. These deposits are seen in joints, synovium and tendon sheaths.

3) Localized Amyloidosis: فرم موضعي

- Senile Amyloidosis:** Affects the vessels of the brain (gray matter) in cases of Alzheimer's disease (senile dementia). The amyloid protein is B2 amyloid protein (AB2 protein).
- Amyloid deposits within endocrine tumors:** e.g. amyloid deposits within medullary carcinoma of thyroid. The amyloid protein is procalcitonin produced by the tumor cells.
- Idiopathic localized amyloid deposits:** may occur in any of several sites as larynx, tongue, urinary bladder, muscles, heart... etc. The amyloid protein is ALL secreted by plasma cells which often exist around the amyloid deposits and therefore this form of amyloidosis is considered a localized form of B cell dyscrasias.

PATHOLOGY OF THE AFFECTED ORGANS:

1) THE KIDNEY: slide 15

Kidney amyloidosis is the most common and the most serious involvement in the disease.

Gross Picture:

- Size: kidney is enlarged but in prolonged cases it may become small (contracted) due to ischemic changes → become blind to death fibrous tissue.
- Cut section: Pale gray waxy amyloid spots are seen. The cut surface is flat and the borders are sharp.
- Firm in consistency.
- Gross staining can be applied:
 - iodine + 1% sulphuric acid → blue stain Amyloid
 - Congo's iodine → dark brown Amyloid

Microscopic Picture:

- Amyloid deposits are seen in:
 - Glomeruli: in the basement membranes of capillaries and in the mesangial matrix. In advanced cases the capillary lumens are obliterated.
 - Tubules: within their basement membranes and peritubular connective tissue.
 - Walls of vessels → vascular narrowing → ischemic contracture of the kidney.
- Amyloid appears homogenous. According to type of stain the appearance will be:
 - Hematoxylin and eosin stain → pink and refractile.
 - Congo red stain → orange red amyloid → apple-green birefringence with polarizing light.
 - Methyl violet stain → metachromatic rose red staining of amyloid, while other tissues are stained violet.

Clinical Effects:

- Nephrotic syndrome:** This is proteinuria (due to glomerular affection) associated with hypoproteinaemia, and generalized edema as well as hyperlipidemia and lipiduria.
- Polyuria** (resembling diabetes insipidus) due to reduced water reabsorption.
- Hypertension and renal failure** in advanced cases.

White Knightstone

Renal → VIP + slide (demonstration)

Flow pink in tubule plus not Amyloid

Flow pink in glomeruli Amyloid

Flow pink in tubule plus not Amyloid

Flow pink in glomeruli Amyloid

Flow pink in tubule plus not Amyloid

Flow pink in glomeruli Amyloid

2) THE LIVER:

Gross picture: Liver is enlarged and firm. Cut section shows pale gray waxy amyloid streaks. The cut surface is flat with sharp borders. Gross staining can be applied.

Microscopic Picture: Amyloid deposits (detected by hematoxylin and eosin stain and by special stains) are seen in the walls of arterioles and venules as well as in the perisinusoidal space (Disse space), then progressively in the sinusoidal walls → sinusoidal narrowing and pressure atrophy of the adjacent liver cells. + Congo red stain

Clinical Effects:

Hepatic dysfunction is usually slight (due to great hepatic reserve) (Liver failure is rare)

3) THE SPLEEN: Two patterns

a) **Sago Spleen (focal or white pulp type):** The splenic lymphoid follicles are affected where amyloid is deposited in the walls of central arterioles → moderate splenomegaly with mottled cut surface by pale gray waxy amyloid spots against the red pulp

b) **Diffuse Amyloid Spleen (diffuse or red pulp type):** The red pulp is affected where amyloid is deposited in the walls of sinusoids → marked splenomegaly with uniformly pale gray waxy cut surface

4) HEART:

May be a localized (usually in old age), or may be a part of generalized amyloidosis. There is moderate cardiac enlargement. The typical pattern is subendocardial amyloid deposits, particularly in the atria. There are also amyloid deposits progressively occurring between the myocardial fibers, causing their pressure atrophy. Heart failure may complicate the condition.

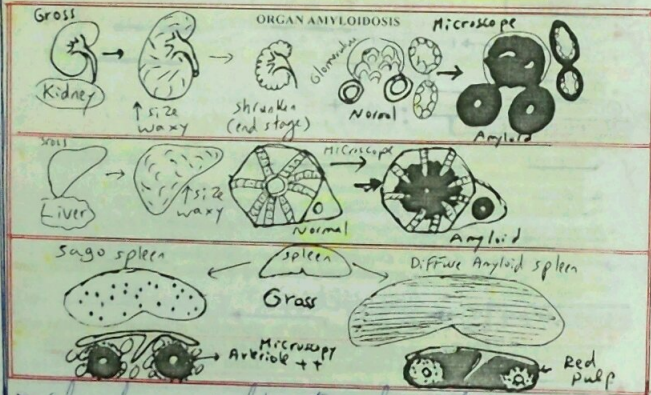
5) THE ENDOCRINE GLANDS:

In cases of generalized amyloidosis, many glands as the pituitary and adrenals may be affected. Clinical effects may not appear except in advanced cases, e.g. Addison's disease due to adrenal amyloidosis. *Excess personal gland function*

6) THE GASTROINTESTINAL TRACT: Any part of the GIT can be affected.

- Tongue affection → macroglossia.
- Intestinal affection → mucosal atrophy, ulcerations, hemorrhages, malabsorption & diarrhea.

7) ANY OTHER ORGAN: (skin, respiratory passages, urinary bladder ... etc)



Clinical pic ⇒ malabsorption + ulcer + bleeding + Atrophy + diarrhea

Supra renal gland → Amyloidosis → acute adison disease

@Bronzed Diabetes

@Gout

طول ما المص
بعض موالين المرض دول

ن

Mucin

→ α_1 → Mucin
Inter
→ α_2 → Hyalomucin

MUCIN MYXOMATOUS DEGENERATION

not Mucoid degeneration

Definition: Pathological accumulation of mucopolysaccharides between connective tissue fibers.

Grossly: The affected tissue appears soft & gelatinous.

Microscopically: Stellate shaped mesenchymal cells, embedded in pale mucinous matrix.

Examples:

- Myxodema.
- Mesenchymal tumors as leiomyoma, schwannoma, chondroma, chondrosarcoma & liposarcoma.

URIC ACID & URATES GOUT

* Puric acid
* Not waste product

gout + uric acid + blood + 650

Definition: Disturbance in purine metabolism, leading to increase of serum uric acid & deposition of sodium urate crystals in tissues.

Aetiology:

- Primary gout. A heterogeneous group with known or unknown enzyme defect. Some cases have hereditary predisposition including a rare sex linked from affecting males (Lesch-Nyhan syndrome).
- Secondary gout due to excess nucleoprotein destruction as in chronic myeloid leukemia.

Pathology:

- Increased serum uric acid (hyperuricemia) above 6 mg % (normal = 3-6 mg %).
- Monosodium urate (MSU) crystal deposition leading to:
 - a) Acute arthritis. Joints (particularly the big toe) are severely inflamed. Microscopically there is dense exudation of neutrophils.
 - b) Chronic tophaceous arthritis. → excess deposition of MSU crystals in cartilage & synovium → chronic inflammation & fibrosis. Joint ankylosis may occur.

* c) Tophi:

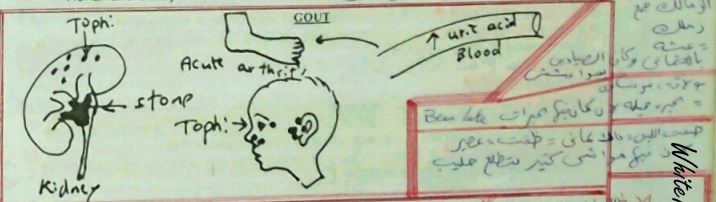
These are small nodular lesions. Structurally they consist of aggregated urate crystals. Microscopically there are deposits of amorphous material surrounded by chronic granulomatous inflammation rich in giant cells (foreign body granuloma).

Sites:

- Joint structures: synovium, tendons, ligaments & cartilage (→ cartilage erosion)
- Cartilage of the nose and ear pinna → ulceration of the overlying skin
- Subcutaneous, particularly in eye lids → ulceration of the overlying skin
- Other sites as cardiac valves & interstitial tissue of kidney → gouty nephropathy

* d) Gouty nephropathy:

- It is characterized by
- Tophi in interstitial tissue of kidneys
- Uric acid/urate stones in pelvis and calyces
- Renal failure may occur.



* Struma = جعشور
* Gout = جوت
* Uric acid = حمض اليوريك
* Blood = دم
* Acute arthritis = التهاب المفاصل الحاد
* Stone = حصاة
* Kidney = كلية
* Tophi = توفات
* Gout = جوت
* uric acid = حمض اليوريك
* Blood = دم

White Knightlane

ectopic

GROWTH DISTURBANCES

Disturbances or disorders of growth may be:

A) CONGENITAL such as:

- **Agensis**: Failure of development of an organ (or part of it) e.g. absent kidney.
- **Hypoplasia**: Undersized organ e.g. hypoplastic kidney and infantile uterus.
- **Aplasia**: This is failure of cell growth. It may represent severe hypoplasia. The affected organ is rudimentary (e.g. rudimentary kidney, rudimentary tooth ...).
- ★ **Other Congenital Anomalies** as **supernumerary organ** (e.g. supernumerary kidney), **organ duplication** (as intestine), **ectopic tissue** (e.g. parathyroid within thymus), **fused organs** (as gonadosplenic fusion).... etc.

B) ACQUIRED: 1) Atrophy 2) Hypertrophy 3) Hyperplasia 4) Metaplasia 5) Dysplasia 6) Neoplasia

ATROPHY

Definition:

Cellular atrophy is acquired shrinkage of cell size due to decreased cell anabolism and/or increased cell catabolism. The cell remains alive with reduced organelles.

Tissue or organ atrophy is decrease in its size and weight after it has reached its full development. This is either due to cell atrophy or cell loss. The atrophic part may be replaced by fibrous tissue or adipose tissue.

Aetiology and Types:

1) **Physiological Atrophy:**

- a) **Localized Atrophy** e.g. atrophy of thymus after puberty & atrophy of mammary glands and ovaries after menopause due to diminished hormone stimulation.
- b) **Generalized Atrophy due to aging** may be physiological or pathological:
 - Physiological aging of cells is an age related disorder (**senile atrophy**), believed to be due to decreased oxidative phosphorylation by the aged mitochondria → decreased energy and decreased capacity of uptake of nutrients.
 - Pathological premature aging (**progeria**): This early (premature) aging in young individuals due to error in DNA replication → reduced cell viability.

2) **Pathological Atrophy:**

- a) **Generalized atrophy**: It affects all tissues and organs (including the brain). Heart is small and shows brown atrophy, skin is wrinkled due to loss of elastic fibers, bones & muscle are weak... etc. Causes include:
 - **Decreased anabolism** in cases of chronic malnutrition and starvation.
 - **Increased catabolism** as in advanced stages of malignancy (cachexia), tuberculosis & thyrotoxicosis.
 - **Progeria** → premature aging.
- b) **Localized atrophy:**
 - **Disuse atrophy**: It is due to decreased workload e.g. atrophy of limb muscles following prolonged immobilization after bone fracture & atrophy of non-functioning renal tubules in case of chronic glomerulonephritis.
 - **Neuropathic atrophy**: It is due to loss of innervation e.g. atrophy of muscles of affected limb in case of poliomyelitis.

CHAPTER V

- **Hormonal atrophy**: It is due to loss of endocrine stimulation e.g. breast atrophy following surgical resection of ovaries.
- **Atrophy due to diminished blood supply**: It includes:

- 1- **Pressure atrophy** due to pressure on the cells and their feeding vessels from outside e.g. atrophy of liver cells in cases of amyloidosis & atrophy of the vertebrae (but not of the avascular intervertebral discs) due to pressure by aortic aneurysm.
- 2- **Vascular atrophy**: This is atrophy of a tissue or organ due to diminished blood supply caused by a vascular disease causing narrowing of the vessels e.g. kidney atrophy due to atherosclerosis of renal artery.
- **Acquired aplasia** (cell loss) which is commonly idiopathic (unknown cause) as testicular germ cell aplasia (Sertoli cell only syndrome) which is a common cause of male infertility and bone marrow aplasia (→ aplastic anemia).

2) HYPERTROPHY

Definition:

Hypertrophy is increase in the size of the cell, consequently leading to increase in the size of the affected tissue or organ. Cell hypertrophy is due to increased protein synthesis & occurs to meet increased functional demands. Pure hypertrophy occurs in muscles, but in other tissues hypertrophy is usually associated with hyperplasia.

Aetiology and Types:

1- **Physiological Hypertrophy**: The best examples include:

- a) Pregnant uterus due to hormone stimulation.
- b) Hypertrophy of striated muscles in muscle builders.

2- **Pathological Hypertrophy:**

- a) **Adaptive type**: It affects the muscle coat of hollow organs due to increased intraluminal pressure. Examples:
 - Left ventricular hypertrophy due to hypertension or aortic valve stenosis.
 - Urinary bladder hypertrophy due to stricture of the bladder neck (caused by bilharziasis, tumor or others).
 - Hypertrophy of intestinal wall in cases of chronic intestinal obstruction.
 - Hypertrophy of stomach in case of pyloric stenosis.
- b) **Compensatory type**: If one of a paired organ is out of function or surgically removed, the other organ undergoes compensatory hypertrophy e.g. kidney enlargement when the other kidney is surgically removed.

3) HYPERPLASIA

Definition:

Hyperplasia is increase in the number of cells, leading to increase in the size of the affected tissue or organ. It is usually accompanied by some degree of hypertrophy. It can occur only in cells capable of division i.e. all cells except nerve cells, skeletal and cardiac muscle cells.

Aetiology and Types:

- 1- **Physiological Hyperplasia**: e.g. mammary glands & genitalia at puberty (physiological hormonal hyperplasia).
- 2- **Pathological Hyperplasia**: Hyperplasia in pathological states includes:
 - a) **Hormonal hyperplasia** e.g. endometrial & mammary hyperplasia due to excessive oestrogen stimulation.
 - b) **Irritation hyperplasia** of lymphoid tissue in response to antigenic stimulation.
 - c) **Compensatory hyperplasia** (considered physiological or pathological). Examples:
 - Bone marrow hyperplasia following hemorrhage or hemolysis.

It is more blessed to give than to receive.

80% mechanism not known

- Hyperplasia of the liver after partial hepatectomy → progressive restoration of the normal liver weight in few weeks. Awareness of liver hyperplasia has encouraged partial liver transplantation, since hyperplasia of the remaining liver in the donor & of the transplanted part in the recipient will restore normal liver size in both. Hyperplasia is stimulated by growth factors (e.g. TGF- α) produced by liver cells. Eventual cessation of cell growth is caused by growth inhibitors (e.g. TGF- β) produced by the non-parenchymal cells of the liver.

Differences between Hyperplasia and Neoplasia:

HYPERPLASIA	NEOPLASIA
- Excited by a stimulus - Reversible, i.e. cell proliferation stops if the stimulus abates. - Proliferated cells are normal-shaped. - May be useful as compensatory hyperplasia.	- A stimulus may not be detected. - Irreversible. i.e. cell proliferation is unlimited & progresses, even if any evoking stimulus has stopped. - Proliferated cells are abnormal-shaped (in case of malignant neoplasia) - Harmful

Although hyperplasia is distinctly different from neoplasia, it may be precancerous i.e. pathological hyperplasia may lead to malignant neoplasia.

4 METAPLASIA

Definition:

Metaplasia is the transformation of one mature differentiated cell type into another of the same category. It is a reversible process that represents adaptive substitution of cells more sensitive to stress by other more resistant cell types that can better withstand the adverse environment. Like hyperplasia, it is precancerous.

Aetiology and Types:

1- Epithelial Metaplasia: The most common examples include:

- Squamous metaplasia:** This is the transformation of columnar or transitional cells into stratified squamous epithelium. This is sometimes followed by leukoplakia.

Examples of Squamous Metaplasia:

- Urinary bladder mucosa in case of bilharzial cystitis.
- Tracheal and bronchial mucosa in smokers or vitamin A deficiency.
- Bile duct epithelium at sites of impacted stones.
- Endocervical mucosa in case of chronic cervicitis. Cancer in female.

Leukoplakia:

- These are thick irregular white mucosal patches, usually related to chronic irritation. They are precancerous lesions that may → squamous cell carcinoma.
- The most common sites are tongue, vulva and urinary bladder.
- Microscopically, leukoplakia appears as hyperkeratotic thick stratified squamous epithelium. The underlying subepithelial layer shows chronic inflammation.
- Leukoplakia either represents squamous metaplasia with keratinization (e.g. in case of leukoplakia of the urinary bladder) or it may represent hyperplasia with keratin formation if it arises in mucous membranes already composed of stratified squamous epithelium (as tongue and vulva).

- Intestinal Metaplasia:** of the gastric mucosa at the edges of peptic ulcers.

Intestinal glands (alkali)

Define Myositis ossificans

- Mesenchymal Metaplasia:** Fibroblasts may become transformed into chondroblasts or osteoblasts; thus producing bone or cartilage in abnormal sites. Therefore, soft tissue ossification can occur in loci of injury.

Localized Myositis Ossificans

- This condition is characterized by muscle necrosis (may be traumatic).
- The damaged muscle is infiltrated by granulation tissue.
- Fibroblasts of the granulation tissue may show osteoblastic metaplasia leading to ossification.
- Old fibrotic tuberculous lesions may also show osseous metaplasia.

- Serosal metaplasia:** Mesothelial cells can change into glandular stratified or other epithelial types. Example in females, the peritoneum may develop endometrial tissue (endometriosis) due to serosal metaplasia.

- Tumor metaplasia:** It may be epithelial metaplasia e.g. glandular carcinoma (adenocarcinoma) may show areas of squamous metaplasia (referred to as adenoacanthoma). Stromal metaplasia (e.g. cartilaginous and/or osseous metaplasia) may occur in some tumors.

Definition:

Dysplasia is a non-neoplastic disordered proliferation of cells; usually induced by prolonged cell irritation. Dysplasia literally means any abnormal growth. It is a microscopic change with no specific gross changes. It chiefly affects epithelial cells.

Microscopic Characteristics:

- It is characterized by loss of uniformity of the individual cells accompanied by loss of their architectural orientation (polarity). Dysplastic cells are atypical looking. They show pleomorphism (variation in size and shape), enlarged dark (hyperchromatic) nuclei and increased mitotic activity.
- Degree of dysplasia:** According to degree of cell atypia and extent of involvement, dysplasia is graded into mild (affecting lower third), moderate (affecting lower two thirds) and severe. Severe dysplasia corresponds to carcinoma in situ (see below), it involves the entire epithelial thickness.
- Dysplasia is encountered principally in the epithelia.

Examples (sites) of dysplasia:

- Cervical dysplasia in females with chronic cervicitis.
- Urothelial dysplasia in patients with bilharzial cystitis.
- Hepatocellular dysplasia in cases of chronic hepatitis and cirrhosis.

Prognosis (Course) of dysplasia:

- Mild and moderate grades of dysplasia that do not involve the entire thickness of the epithelium are commonly reversible when the cause is removed. However they may progress to severe dysplasia.
- Severe dysplasia (carcinoma in situ) is highly precancerous (preinvasive). In time almost all cases progress to invasive cancer.

Remark:

Dysplasia literally means any abnormal growth. Therefore the term is sometimes used to describe certain congenital defects, such as fibrous dysplasia of bone and renal dysplasia. These types of dysplasia are not related to the conventional epithelial dysplasia described above.

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freely you have received; freely give.

Sever dysplasia (CIS) **CARCINOMA IN SITU**
(Intraepithelial Neoplasia Intraepithelial Carcinoma, Pre-invasive Carcinoma)

Definition:

Carcinoma in situ (CIS) represents a preinvasive stage of cancer & is characterized by severe epithelial atypia (severe dysplasia) without invasion of the basement membrane. CIS is essentially a microscopic change. Once the basement membrane is invaded the CIS phase ends and actual (invasive) malignant tumor starts.

Pathological Features:

Gross features:

- CIS may be difficult to detect grossly.
- However it may cause a thick indurated patch (as CIS of cervix or bladder).
- Rarely CIS may cause a mass as in cases of CIS of mammary ducts.

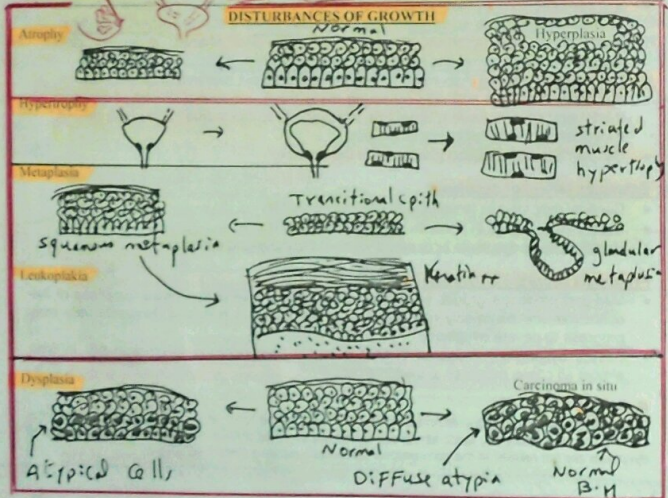
Microscopic features: CIS is essentially a microscopic change characterized by:

- Diffuse cellular atypia involving the whole thickness of the affected epithelium. The cells are pleomorphic with dark nuclei and numerous mitoses i.e cytologically malignant. Their architectural orientation (polarity) is disturbed.
- No invasion of basement membrane

Rate: Progression into invasive carcinoma occurs after a variable time (usually years).

Examples of common sites of CIS

- 1- Mammary gland 2- Bladder 3- Cervix & endometrium 4- GIT 5- skin



Acquired growth disturbance

CHAPTER VI

NEOPLASIA (TUMORS)

DEFINITION

A neoplasm (tumor) is a new growth forming an abnormal mass, caused by autonomous self-controlling proliferation of cells independent of stimuli. The study of tumors is referred to as oncology.

GENERAL CHARACTERISTICS OF TUMORS

Tumor proliferation is uncontrolled (does not follow the rules of normal cell growth) e.g.

- Tumors can be derived from any cells, even from cells that do not normally divide (nerve cells and striated muscle cells).
- Tumors continue proliferation even if the patient is starved.
- Cell proliferation is irreversible and unlimited. Thus cell proliferation progresses even after cessation of any evoking stimuli. Example lung carcinoma will continue growing even if the patient stops smoking.

Tumor proliferation has no useful function

Some tumor cells may function in a harmful way e.g. tumors of neuroendocrine origin may secrete hormones.

Any neoplasm has two basic components:

1. The transformed (neoplastic) cells:

- a) The vast majority of tumors arise from a single transformed cell i.e. monoclonal.
- b) Few tumors are polyclonal; i.e. the neoplastic cells are descendants of many transformed cells.

2. The supporting stroma & vessels

consist of non-transformed elements derived from the host in response to factors released from the tumor e.g. angiogenesis factor.

CLASSIFICATION OF TUMORS

A) ACCORDING TO THEIR BEHAVIOR (BIOLOGICAL CLASSIFICATION)

- 1) Benign neoplasms (generally have good prognosis). See table below
- 2) Malignant neoplasms (generally have poor prognosis). See table below
- 3) Intermediate tumors (locally malignant neoplasms locally aggressive tumors)

B) ACCORDING TO TISSUE OF ORIGIN (HISTOLOGICAL CLASSIFICATION)

- 1) Epithelial tumors
- 2) Mesenchymal tumors
- 3) Others

Neoplasm
* General characteristics
→ Uncontrolled
→ no useful function
→ Two basic components
→ transformed cells
→ supporting stroma & vessels
Phytotoxins
Adenoma

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Benign * Hamartoma
slow growth rate *
fibrous caps *
stop growth after puberty
non caps

CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS

BENIGN NEOPLASMS	MALIGNANT NEOPLASMS
A) TUMOR BEHAVIOR 1-Rate of Growth: Often slow. X 2-Mode of Growth: non invasive Expansile, i.e. compressing the surrounding tissues without invasion. 3-Prognosis: = behaviour a) Benign tumors do not spread b) Benign tumors do not recur if well excised. c) Benign tumors are not dangerous unless: They arise in vital organs as brain. They arise in hollow organs (as intestine) causing obstruction. They produce hormones as in tumors of endocrine glands. Some benign tumors may change malignant. This may be clinically manifested by change of growth rate (becoming faster) and growth mode (becoming infiltrative, destructive and metastasizing). It is pathologically manifested by change of the gross pattern including capsular invasion, necrosis & hemorrhage, and change of microscopic pattern including loss of cellular & histological differentiation). N.B. Benign Tumors produce hormone only if occuring in gland ≠ Para neoplastic syndrome of malignant	A) TUMOR BEHAVIOR 1-Rate of Growth: Often rapid. ✓ 2-Mode of growth: Invasive, i.e. infiltrating and destroying the surrounding normal tissues. Some degree of expansion also exists. 3-Prognosis: a) Malignant tumors spread (see later) b) Recurrence after surgical excision is very common either from tumor cell remnants (not removed with the excised tissue) or from a new neoplastic transformation. c) Malignant tumors are serious & cause death. Causes of Death include: 1. Local organ destruction by direct spread. 2. Distant organ destruction by metastases. 3. Destruction of vital centers (brain tumors). 4. Obstruction of the lumen of hollow organs e.g. intestinal tumors. 5. Organ failure e.g. renal failure. 6. Renal failure due to urinary obstruction (or bilateral renal tumors). 7. Liver failure & jaundice in case of primary or metastatic liver tumors. 8. Malnutrition due to: - Loss of appetite - Interference with food intake (in cancer of GIT) 9. Chronic toxemia due to secondary bacterial infection. 10. Anaemia is common due to: - Recurrent hemorrhages from the tumor. - Bone marrow destruction by metastases. - High tumor cell metabolism may lead to folic acid deficiency. Iron deficiency may also occur. - Autoimmune hemolysis in some cases. 11. Cachexia (wasting & weakness) due to anaemia, toxemia, malnutrition, organ failure. 12. It is manifested by marked decrease of body weight accompanied by profound weakness, anorexia & anaemia. The

benign Tumour in brain more dangerous than Malignant Tumour in skin

* Define Anaplasia?

Malignant Tumour
Produce hormones without acciding in glands
Define Cachexia?
Define para neoplastic syndrome?

body resistance is lowered & infections as pneumonia may terminate the patient's life.
Recently, it has been shown that TNF (released from activated macrophages) may play an important role in cachexia since it suppresses the patient's appetite & interferes with fat metabolism.
Para-neoplastic syndromes occur in 10% of cases. They are caused by abnormal products of the tumor e.g. ACTH causing Cushing's syndrome

B) TUMOR STRUCTURE

1-GROSS FEATURES:
 • Tumor margins are well defined.
 • Cut section of the tumor is commonly uniform with no hemorrhage or necrosis.
 • A tumor arising inside a solid organ appears globular or ovoid & often becomes surrounded by a fibrous capsule composed of a rim of condensed connective tissue.
 • A tumor arising from surface epithelia form a non-capsulated polyp (papilloma).

B) TUMOR STRUCTURE

1-GROSS FEATURES:
 • Tumor margins are irregular or ill-defined.
 • Cut section of the tumor often shows areas of hemorrhage and necrosis.
 • A tumor inside a solid organ appears as an irregular (noncapsulated mass). However, very rarely a malignant tumor may acquire a capsule (mostly incomplete & microscopically shows frequent foci of tumor invasion).
 • Tumors arising from surface epithelia appears as noncapsulated masses assuming different patterns:
 - Polypoid fungating cauliflower-like mass bulging over the surface. The base of the mass shows some infiltration under the surface.

2-MICROSCOPIC FEATURES:
 a) Cell Differentiation:
 Cellular differentiation is the extent to which tumor cells resemble comparable normal cells. In benign tumors the cells are perfectly differentiated i.e. closely mimic the corresponding normal cells. Rare mitoses.

2-MICROSCOPIC FEATURES:
 a) Cellular Anaplasia:
 This is abnormal differentiation. Malignant cells show grades of cellular atypia referred to as anaplasia ranging between mild anaplasia & marked anaplasia characterized by:
 • Cellular pleomorphism: malignant cells vary in size & shape. However some tumors are monomorphic.
 • Nuclear pleomorphism: Nuclei may be irregular or bizarre shaped.
 • Nuclear enlargement & hyperchromatism: Due to increased synthesis of DNA, the nuclei appear dark (hyperchromatic) & the nucleocytoplasmic (N/C) ratio is increased approaching 1:1 (normally N/C ratio is approximately 1:5).

* Define Anaplasia?
 * Define Cachexia?
 * Define para neoplastic syndrome?
 * Define Gross features?
 * Define Microscopic features?
 * Define Cell Differentiation?
 * Define Cellular Anaplasia?
 * Define Cellular pleomorphism?
 * Define Nuclear pleomorphism?
 * Define Nuclear enlargement & hyperchromatism?

body resistance is lowered & infections as pneumonia may terminate the patient's life.
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* Size & shape
 * Nucleus

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Para-neoplastic syndromes occur in 10% of cases. They are caused by abnormal products of the tumor e.g. ACTH causing Cushing's syndrome

Write tonight

Discuss cellular Anaplasia in Malignant Tumour

- Nucleoli may be prominent
- Abundant mitoses & frequently abnormal mitotic figures (e.g. tripolar spindles).
- Tumor giant cells containing a single large polyploid nucleus or multiple nuclei.

b) Histological Differentiation:

In benign tumors the tumor cells exhibit structural patterns similar to the normal tissue. Thus adenoma of thyroid consists of acini almost similar to those of normal thyroid

b) Histological Differentiation:

- This is the degree of resemblance of the structural pattern of the tumor to that of the normal tissue.
- Carcinoma may be graded as well differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III) & undifferentiated (grade IV). Better differentiated tumors tend to show less marked cellular anaplasia & grow slower. On the other hand undifferentiated tumors show great cellular anaplasia & grow faster. Undifferentiated (grade IV) carcinoma is sometimes termed anaplastic carcinoma

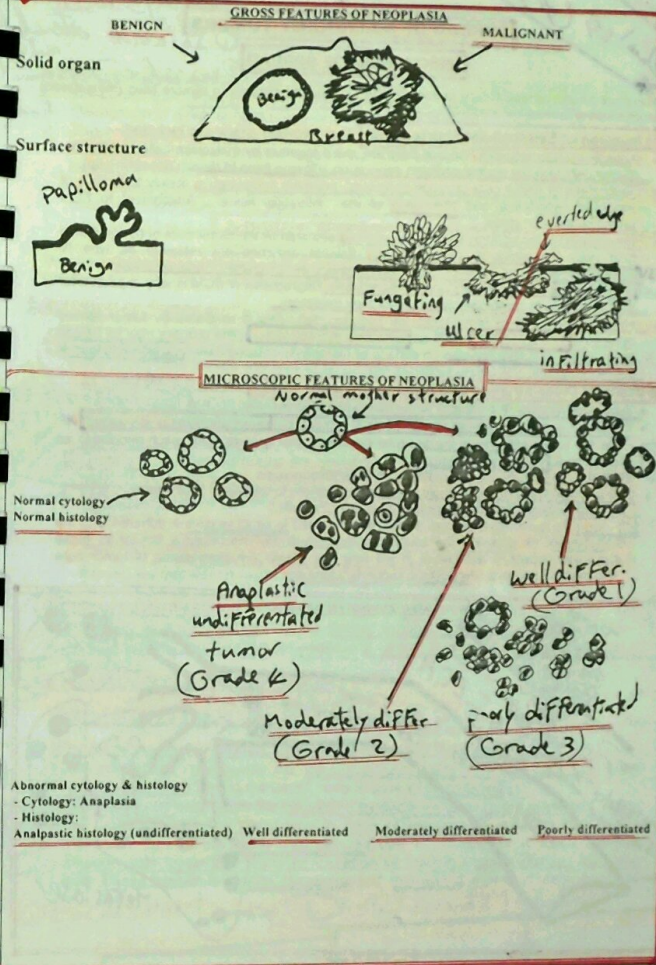
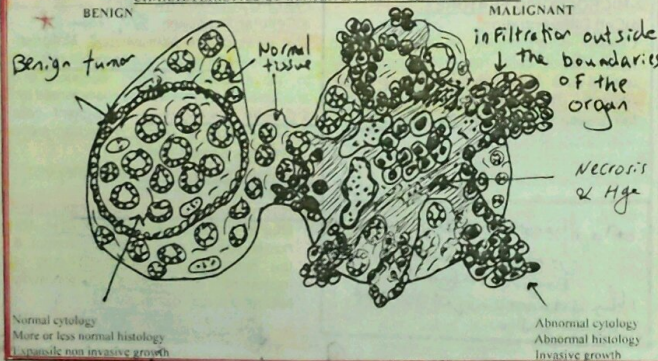
c) Other Features:

- The tumor has stroma containing few vessels.
- Secondary changes as myxoid or hyaline change may occur, but necrosis and hemorrhage are extremely exceptional.

c) Other Features:

- The tumor stroma is rich in vessels which may be sometimes thin-walled.
- Secondary changes may occur, and foci of hemorrhage and necrosis are common.

CHARACTERISTICS OF BENIGN & MALIGNANT NEOPLASIA



Factors Influence Prognosis of Malignant Tumours

P. 87 & 15

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SPREAD OF MALIGNANT TUMORS

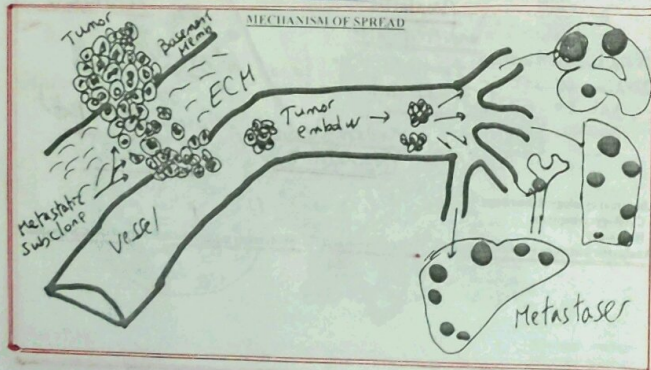
MECHANISM OF SPREAD

Malignant tumors spread locally to surrounding tissues and distantly to remote sites (metastases). Mechanism of spread includes:

- 1. Invasion of Extracellular Matrix (ECM):** The following steps are included:
 - Loss of cellular cohesion. Normal cells are glued together by molecules called **cadherins**. Tumor cells lose the normal cadherin expression, allowing them to detach (loosening up).
 - Attachment of tumor cells (through receptors) to matrix components, mainly to laminin of basement membrane and **fibronectin** of the interstitial tissue. Attachment to ECM promotes the next steps.
 - Degradation of the ECM by proteolytic enzymes secreted by the tumor cells or by stimulated host cells (fibroblasts & macrophages). Several enzymes are released as type IV collagenase (causing lysis of basement membranes of epithelia and of vessels) and **elastinase** (causing degradation of interstitium). Degradation of ECM is very important for the tumor cells to create passageways for their migration.
 - Migration (mobility) of tumor cells (by pseudopodia). This is mediated by tumor-derived cytokines (mobility factors) such as **autocrine mobility factor**. The process may be helped by acquiring negative charges on surface of tumor cells causing their repulsion and loss of contact inhibition.

2. Vascular Dissemination and Homing of Tumor Cells:

- Tumor cell mobility → contact of tumor cells with blood vessels.
- Tumor cells penetrate lymphatics, capillaries & venules, but rarely arterioles (thick-walled).
- Once the tumor cells cross the vascular basement membranes, they reach circulation as tumor emboli. Fate of tumor emboli:
 - Most tumor emboli are destroyed by immune mechanisms.
 - The surviving tumor cells (single or in clumps) adhere to platelets. This affords them some protection from antitumor host immune cells.
 - Finally, the surviving tumor cell emboli get impacted in small vessels → adherence to the endothelium → crossing the basement membrane (by mechanisms similar to those described above) → settlement in the new site (homing) → proliferation of tumor cells → metastatic deposits (metastasis, secondary tumors).



Give an account on Lymphatic spread → more common in carcinoma than sarcoma than low BV.
② → embolism
→ Permeation eg. breast

ROUTES OF SPREAD

1. LOCAL (DIRECT) SPREAD

- Malignant cells spread in all directions along lines of least resistance. Some structures as cartilage, perosteum & elastic tissue delay direct spread. Mechanism of direct spread (invasion of ECM): see above.
- Direct spread to a surface (skin or mucosa) leads to ulceration (malignant ulcer). Direct spread from one hollow organ to another adjacent one causes a malignant fistula (e.g. between rectum and vagina).
- Some tumors may spread along the perineural space, e.g. **prostatic carcinoma** causing severe pain.

2. DISTANT SPREAD (METASTASIS)

Metastasis: development of secondary malignant implants, discontinuous with the primary tumor can occur by many routes, the most common of which is lymphatic & vascular spread

A) LYMPHATIC SPREAD: Occurs more commonly with carcinomas than sarcomas:

1) Lymphatic Embolism:

- Malignant cells invade the wall of lymphatic vessels. Detached cells are carried as tumor emboli with lymph.
- Tumor emboli are arrested in the **subcapsular sinus** of the lymph node. The malignant cells proliferate & gradually destroy & replace the node.
- Spread from one node to another may occur by efferent lymphatics.
- Grossly, the affected nodes are enlarged & firm. Cut surface appears grayish white. If lymph node capsules are infiltrated, the nodes become fixed.
- Microscopically, the metastatic deposit resembles the primary tumor from which it is derived.
- Progressive spread by the lymphatic route may ultimately lead to tumor emboli within the main lymphatic ducts (thoracic duct), from which tumor emboli reach the venous circulation causing **hematogenous spread**.

- 2) Lymphatic Permeation:** Sometimes, malignant cells grow inside the lumen of lymphatics as solid columns causing marked lymphatic obstruction and lymphatic oedema. Breast carcinoma is an example of tumors that commonly permeate the lymphatics.

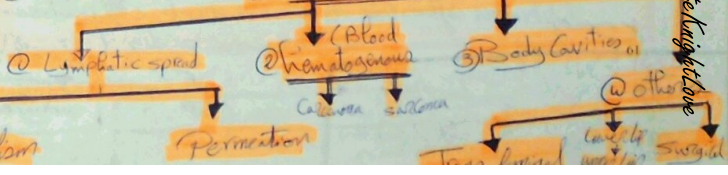
B) HEMATOGENOUS (BLOOD) SPREAD:

Pattern of blood spread in sarcoma & carcinoma. See later

Way & mechanism by which malignant cells reach the blood:

- Malignant cells may reach the venous circulation through thoracic duct (after lymphatic spread). This is the usual way in case of carcinoma.
- Malignant cells may reach the circulation by direct invasion of blood vessels within the tumor. This is the usual way in case of sarcoma. It is worth noting that malignant tumors are richly vascularized due to release of a tumor derived angiogenesis factor that leads to formation of feeding vessels derived from the host. These vessels are more numerous and thin-walled in case of sarcomas.

Local Direct → Distant spread (Metastasis)



* Carcinoma in distant metastases first appear ?? in Liver
* if patient has prostatic tumor $\rightarrow$ 8 appear metastases in brain where also metastases appear $\rightarrow$ lungs

Course of tumor emboli depends on anatomical factors:

- Emboli derived from primary tumors of organs drained by **systemic veins (vena cava)** e.g. breast, skin and kidney, are carried through pulmonary arteries to lungs causing lung metastases.
- Emboli derived from tumors of lungs (whether primary or metastatic) are carried through **pulmonary veins** to left side of heart $\rightarrow$ **systemic arterial circulation** to metastases in different organs as liver, bones, brain...etc.
- Emboli derived from tumors of organs drained by the **portal vein (tumors of gastrointestinal tract)** are carried to liver causing liver metastases. Further spread from liver gives rise to emboli that reach the hepatic veins and consequently to the inferior vena cava to lungs...etc.
- Emboli reaching the **vertebral system of veins** from tumors of pelvic, abdominal or thoracic organs leads to metastases in brain, spinal cord and vertebrae without causing lung metastases. This is because the vertebral veins have wide anastomotic channels connecting them with the lumbosacral, abdominal and thoracic veins.

Pathology of organ metastases:

- The most common sites of metastases are the liver, lungs, bones & brain.
- Metastases are rare in muscles, spleen, pancreas & intestine.
- Gross picture:** Metastases appear as scattered round nodules of variable sizes.
- Microscopic picture:** Metastases resemble the primary tumor from which they are derived.
- Bone metastases:**
 - It is common in carcinomas of thyroid, breast, lung, prostate & kidney.
 - It develops in vascular bone sites (ends of long bones, vertebrae, ribs, sternum, pelvis & skull).
 - Bone metastases are commonly **osteolytic**.

In case of cancer prostate it may be osteosclerotic new bone formation is stimulated around the metastatic deposit, since malignant cells of prostatic origin secrete phosphatase.

Effects of bone metastases include

- pathological fracture
- severe pain
- bone marrow destruction leading to anemia, leucopenia & thrombocytopenia

C) SPREAD THROUGH BODY CAVITIES (TRANSCOELOMIC SPREAD)

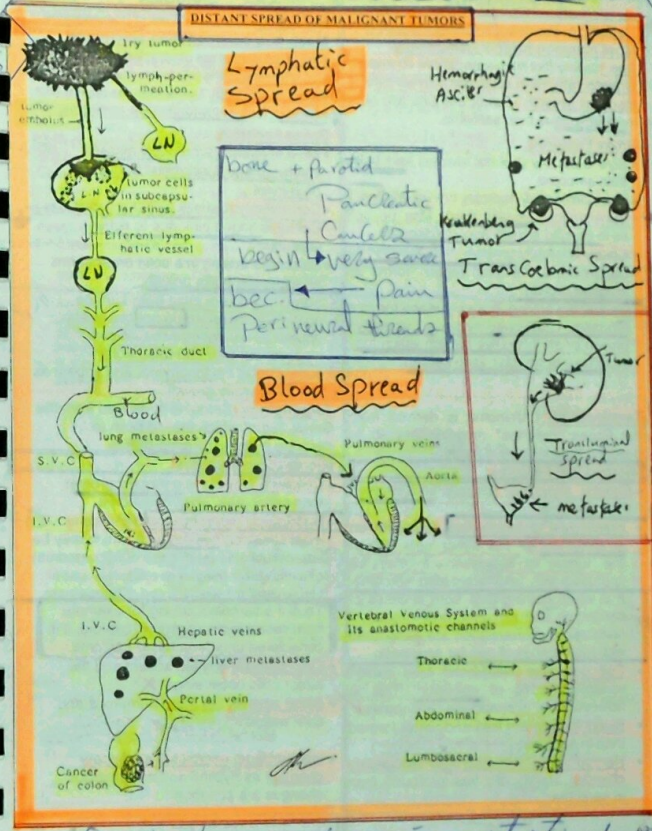
When the **serosal covering** of an organ is infiltrated by malignant cells of a tumor within this organ, some of these cells may detach and become implanted in other sites. This may be associated with **hemorrhagic effusion**. Transcoelomic spread includes:

- Trans-peritoneal spread** from carcinoma of stomach, colon, pancreas...etc $\rightarrow$ metastatic peritoneal/omental nodules accompanied by **hemorrhagic ascites**.
- Krukenberg tumors** In females, carcinoma of stomach (or colon) may be associated with bilateral ovarian metastases termed "Krukenberg tumors" which were thought to represent transcoelomic spread. They are now believed to be due to retrograde lymphatic or blood spread, since Krukenberg tumors can also occur in case of cancers of breast, urinary bladder & biliary tract.
- Trans-pleural and trans-pericardial spread** from lung or breast carcinoma causes metastases on the diaphragm accompanied by hemorrhagic pleural or pericardial effusion.
- Trans CSF spread** may occur in malignant tumors of brain $\rightarrow$ metastases within the walls of ventricles, base of skull and spinal cord.

* **serofibrinous inflammation** $\rightarrow$ serous memb. e.g. peritoneum
 $\rightarrow$ **hemorrhagic ascites** (ascites)

OTHER METHODS OF SPREAD:

- Transluminal implantation** malignant cells detached from transitional carcinoma of the renal pelvis may become implanted in the mucosa of urinary bladder forming secondary deposits.
- Surgical implantation** Instruments contaminated with malignant cells during surgical management of a tumor may transfer tumor cells into the surgical wound causing secondary tumor deposits.
- Implantation from carcinoma of lower lip may lead to a secondary tumor in the upper lip.



* **How to know Liver is metastasized or**
Liver Tumour **metastatic source of tumour**
Diffuse nodules **unilateral blood vessels**

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CHARACTERISTICS OF CARCINOMA AND SARCOMA

The characteristics of the most two common types of malignant tumors (carcinoma and sarcoma) are listed in the following table. The characteristics of other types of malignancy as lymphoma & CNS tumors will be discussed in systemic pathology.

90% CARCINOMA	10% SARCOMA
Definition: Malignant tumor of epithelium Most common form of malignancy Age: Usually (but not always) above 40 years. Growth rate: rapid but slower than sarcoma. Mode of growth: Tumor margins are often more infiltrative than sarcoma.	Definition: Malignant tumor of mesenchyme Much less common than carcinoma Age: Usually (but not always) below 20 years. Growth rate: generally faster than carcinoma Mode of growth: Tumor margins appear less infiltrative & more expansive than carcinoma.
Gross Features: • Size is usually (but not always) less bulky than sarcoma. • Haemorrhage & necrosis are usually less . • Consistency: Usually hard . May be soft as in mucoid & medullary carcinomas. • Colour is usually grayish . • Carcinoma in a solid organ forms an irregular growth.	Gross Features: • Most sarcomas form bulky masses . • Haemorrhage & necrosis: Usually prominent . • Consistency: Usually soft and fleshy . • Colour is tinged pink due to richer vascularity. • Sarcomas arising in a solid organ forms an expansile bulky growth .
• Carcinoma arising from a surface forms a fungating cauliflower mass , an ulcerative growth or an infiltrative pattern which may be diffuse or annular (see before).	• Sarcomas do not arise from surface epithelium therefore do not classically appear as ulcerating or cauliflower masses, but they can arise from subepithelial mesenchyme, and appear as bulky expansile growth.
Terminology: Carcinoma is derived from the Greek "carcinos" meaning a crab to describe their infiltrative mode.	Terminology: Sarcoma is derived from the Greek "sarx" which means flesh to describe their fleshy consistency.
Microscopic Features: • Cellular anaplasia: Usually less marked than sarcoma. • Histological differentiation: depends on arrangement of the tumor cells. When the tumor is anaplastic , it may be copified with undifferentiated sarcoma. It is worth noting that, both in cases of carcinoma and sarcoma, poor grades of histological differentiation are associated with high grades of cellular anaplasia.	Microscopic Features: • Cellular anaplasia is generally greater than sarcoma. than carcinoma. • Histological differentiation depends in most cases on cell products which may be intracellular (as fat in case of liposarcoma) or extracellular (matrix) as collagen in case of fibrosarcoma and osteoid in case of osteosarcoma.
• Cell cohesion: Neoplastic cells exhibit variable grades of cohesion. This is however poor in anaplastic carcinomas. • Blood vessels are less and better formed than in sarcoma. • Hemorrhage, necrosis & secondary changes are usually less profound than in sarcoma.	• Thus if a sarcoma arising for example from osteoblasts, shows no osteoid , it is considered undifferentiated sarcoma. • Cell cohesion is often absent and the tumor cells occur singly. • Blood vessels are more numerous and thin-walled. • Hemorrhage, necrosis & secondary changes as hyaline and myxomatous changes are common.

Carcinoma	Sarcoma
Distant spread • Usually slower than sarcoma. • Occurs early by lymphatics then later by blood . However, some carcinomas spread relatively early by blood (carcinoma of thyroid, breast, lung, kidney, prostate & placenta).	Distant spread • Usually faster than carcinoma. • Occurs early by blood & rarely (10%) by lymphatics .
Staging of carcinoma: TNM system: This is the most popular system for cancer staging. T: represents tumor size & size, graded as T1 (tumor in situ), T1, T2 T3 & T4. N: represents the degree of spread to lymph nodes and is graded as N0, N1, N2 & N3 (N0 means absent). M: represents metastases due to blood spread and is graded as M0 (absent) or M1 (present). Examples T1N0M0 is early cancer stage (better prognosis), while T4 N3 M1 is an advanced stage (worst prognosis).	Staging of sarcoma: TNM system (modified): T: usually graded as T1 or T2 according to size. N: usually graded as N0 & N1. M: graded as M0 & M1.

REMARKS:

- Carcinomas arise from epithelium. The normal epithelium is characterized by cohesive (adherent) cells resting on basement membranes. The type (differentiation) of normal epithelial tissue is determined by cell type & cell arrangement (e.g. glandular or stratified).
- On the other hand sarcomas arise from mesenchyme. The normal mesenchyme mostly consists of noncohesive spindle cells. The type (differentiation) of mesenchyme is largely determined by cell products which may be extracellular as collagen (fibroblasts) & osteoid (osteoblasts) or intracellular as actin & myosin (muscle cells) & fat (lipoblasts). However, some mesenchymal structures have basement membranes (as vascular endothelium).
- It is to be remembered that carcinoma may have an in situ phase not invading the basement membrane, but practically sarcoma in situ does not exist.

CARCINOMA	SARCOMA
Gross Patterns of Carcinoma	Gross Pattern of Sarcoma
Histological patterns of Carcinoma	Histological patterns of Sarcoma
INVASIVE PROPERTY OF DIFFERENT TUMOR TYPES	
Benign (no invasion) 	Carcinoma in situ (no invasion, but ready for it)
Locally malignant tumor (local but no distant invasion) 	Malignant tumor (local & distant spread)

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Benign & OMA

Give an Account $\pm$ on

CHARACTERISTICS OF INTERMEDIATE TUMORS

(LOCALLY MALIGNANT TUMORS, TUMORS OF ERRATIC BEHAVIOR)

Definition

These tumors are characterized by:

1. A slower rate of growth than frank malignant tumors.
2. Local invasion without distant spread (no metastases)
3. Proliferating tumor cells usually show low grade atypia

Prognosis: Much better than malignant tumors. However:

1. Local recurrence after surgical excision is common
2. They may rarely change into frank malignant tumors that metastasize.

Examples of intermediate/ locally malignant tumors:

1. Basal cell carcinoma.
2. Giant cell tumor of bone (osteoclastoma)
3. Adamantinoma from mandible
4. Some neuroendocrine tumors as carcinoid tumor.
5. Chordoma
6. Some tumors of CNS as craniopharyngioma

HISTOLOGICAL CLASSIFICATION OF TUMORS

Tissue of Origin	Benign	Malignant
A) EPITHELIUM:		
1-SURFACE EPITHELIUM:		
a) Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
b) Transitional	Transitional cell papilloma	Transitional cell carcinoma
c) Ducts of glands	Duct papilloma	Duct carcinoma
d) Mucosa of GIT	Adenomatous polyp	Adenocarcinoma
2-GLANDULAR EPITHELIUM		
Endocrine & Exocrine glands.	Adenoma	Adenocarcinoma
B) MESENCHYME:		
1-CONNECTIVE TISSUE		
a) Fibrous	Fibroma	Fibrosarcoma
b) Adipose	Lipoma	Liposarcoma
c) Primitive mesenchyme	Myxoma	Myxosarcoma
d) Bone	Osteoma & osteoblastoma	Osteosarcoma
e) Cartilage	Chondroma, osteochondroma	Chondrosarcoma
2-SMOOTH MUSCLE:		
3-STRATIATED MUSCLE		
4-ENDOTHELIUM		
5-MESENCHYME		
6-Synovium		
	Leiomyoma	Leiomyosarcoma
	Rhabdomyoma	Rhabdomyosarcoma
	Angioma	Angiosarcoma
	Rare	Mesothelioma
	Rare	Synovial sarcoma
C) OTHERS e.g.:		
1-Pigmented cells	Nevus (benign melanoma)	Malignant melanoma
2-Totipotent cells	Teratoma, mature (benign)	Teratoma, immature & malignant
3-Embryonic cells	...	Embryonic tumors
4-Lymphoid & hemopoietic	...	Lymphoma & leukemia
5-Schwann cells	Schwannoma	Malignant schwannoma
6-Trophoblast	Vesicular mole	Choriocarcinoma
7-Neurilia	Example: Astrocytoma grade I	Example: Astrocytic tumors grade II, III & IV
8-Mixed origin	Example: Adenofibroma	Carcinosarcoma

epithelial origin $\rightarrow$ Surface $\rightarrow$ Papilloma
 $\rightarrow$ Glandular $\rightarrow$ Adenoma

Benign = no Metastasis
VIP

BENIGN EPITHELIAL TUMORS

1-PAPILLOMA = finger like tumor

- A benign tumor of surface epithelium. Papillomas are uncapsulated classically exophytic (projecting) papillary tumors, composed of proliferated epithelial cells resting on intact basement membranes, supported from below by connective tissue cores containing blood vessels. Papillomas are rarely inverted endophytic lesions (that push the basement membrane and grow inwards, compressing the subepithelial tissues; of course without invasion) e.g. inverted papillomas of urinary bladder & nose. Classical papilloma may be sessile or pedunculated, single or multiple.
- Papillomas are classified according to type of epithelium into:

A) SQUAMOUS CELL PAPILLOMA

- Definition & origin: A benign tumor of stratified squamous epithelium
- Sites: Skin, lip, tongue, oral mucosa, pharynx, larynx, oesophagus, cervix, vagina & anal canal.
- Gross Picture: A small sessile or pedunculated projection. With progressive tumor growth, its surface becomes thrown into branching folds $\rightarrow$ complex papillary pattern.
- Microscopic Picture: The tumor consists of connective tissue cores covered by thick proliferated stratified squamous epithelium exhibiting acanthosis (increased prickle cell layers) and hyperkeratosis.
- Complications: May rarely change into squamous cell carcinoma.

B) TRANSITIONAL CELL PAPILLOMA (VILLOUS PAPILLOMA)

- Definition & origin: A benign tumor arising from urothelium (transitional mucosa of urinary tract). It is strongly pre-malignant.
- Sites: Urinary bladder, ureter or renal pelvis.
- Gross Picture: The tumor appears as a noncapsulated velvety friable mass of delicate papillary processes.
- Microscopic Picture: Delicate vascularized connective tissue cores covered by usually more than six layers of regular transitional cells.
- Complications: Bleeding (hematuria). Malignant change into transitional cell carcinoma. Bladder neck, urethral or ureteric obstruction.

C) COLUMNAR CELL PAPILLOMAS

These are papillomas arising from columnar epithelium. Two subtypes

1-DUCT PAPILLOMA

- Definition & origin: A benign tumor arising from the epithelium of major ducts.
- Sites: Major ducts, as those of breast (most common) or pancreas.
- Gross Picture: Appears as a small complex papillary projection inside the duct lumen.
- Microscopic Picture: Delicate vascular cores covered by regular ductal epithelial cells.
- Complications: Bleeding per nipple. Malignant transformation into duct carcinoma.

2-MUCOUS CELL PAPILLOMA (Adenomatous polyp, adenopapilloma, mucosal adenoma)

- Definition, origin and Sites: A common benign tumor of glandular mucosa. It grossly appears as papilloma (being projecting from the mucosal surface) and structurally appears as adenoma (being composed of proliferated mucosal glands) and hence it is commonly known as adenomatous polyp, adenopapilloma or mucosal adenoma.
- Sites: Gastrointestinal tract is the commonest site.

Adenoma = benign tumor of glandular origin

① origin ② site ③ Gross ④ Microscopic ⑤ Complication

Covered by keratin + connective tissue core

White Knight Lane

It is more blessed to give than to receive.

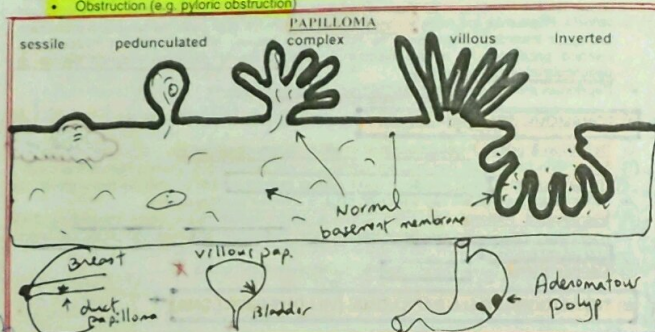
In breast $\rightarrow$ Adenoma $\rightarrow$ acini

Gross Picture: It appears as a sessile, pedunculated or complex papillary projection.

Microscopic Picture: Proliferated mucosal glands lined by columnar epithelium, supported by fibrovascular stroma.

Complications:

- Gastrointestinal bleeding is common.
- Malignant transformation $\rightarrow$ adenocarcinoma.
- Obstruction (e.g. pyloric obstruction)



2- ADENOMA

2- Adenoma / Benign Capsulated

VIP

Definition origin:

A benign tumor arising from glandular epithelium (acini and/or small ducts).

Sites:

- **Exocrine or endocrine glands** (breast, ovary, salivary glands, pancreas, thyroid, pituitary, adrenal glands... etc)
- **Mucosal glands:** e.g GIT & endometrium (mucosal adenoma, adenomatous polyp) (see above)

Gross Picture: A capsulated globular or ovoid mass. Cut section may be solid, cystic or cystic with small projecting papillae.

Microscopic Picture: Several Patterns:

- **Simple adenoma (tubular adenoma):** Consists of proliferated glands lined by cuboidal or columnar epithelium, separated by fibrovascular stroma. Example: Pancreatic adenoma.
- **Fibroadenoma:** Consists of glandular & wide stromal proliferations. Breast is the main site.
- **Cystadenoma:** In some types of adenoma, secretions are retained leading to cystic dilatation of the proliferated acini. Example: Ovarian cystadenoma.
- **Papillary Cystadenoma:** It is a cystadenoma in which the epithelial lining of the cyst proliferates forming papillae. Example: Papillary cystadenoma of the ovary.
- **Special types e.g.:**

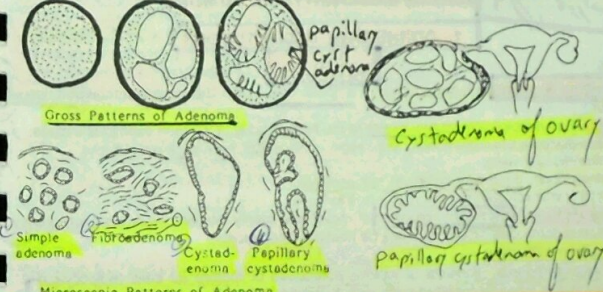
- Pleomorphic adenoma** of major or minor salivary glands in which the adenomatous elements are associated with proliferation of myoepithelial cells, together with excess stromal mucin and metaplastic cartilaginous islands.
- Papillary cystadenoma lymphomatosum (Warthin's tumor)** which also occurs in salivary glands and differs from ordinary papillary cystadenoma in two features: eosinophilic (oncocytic) epithelium & lymphocyte rich stroma.

Complications:

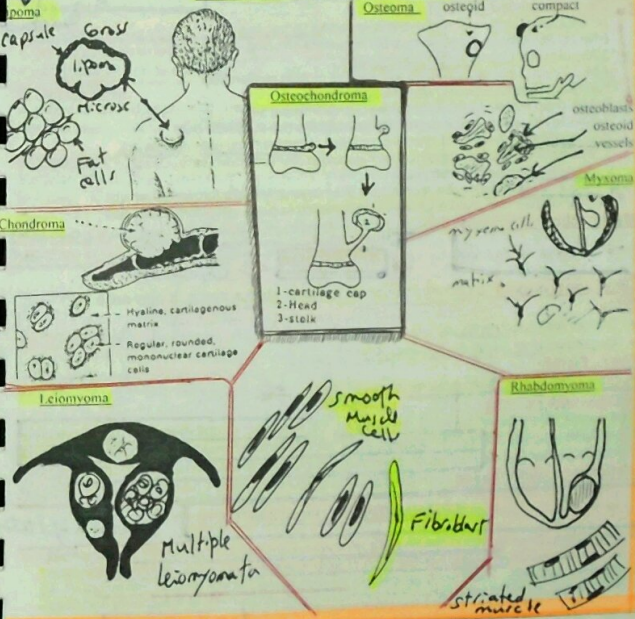
- Adenoma of endocrine glands may function e.g. thyroid adenoma may $\rightarrow$ thyrotoxicosis.
- Malignant change $\rightarrow$ adenocarcinoma.

most common in pituitary gland $\rightarrow$ GH $\rightarrow$ Acromegaly + Gigantism

Solid cystadenoma ADENOMA



Microscopic Patterns of Adenoma BENIGN MESENCHYMAL TUMORS



White Knightlane

Freely you have received; freely give.

BENIGN MESENCHYMAL TUMORS

1- CONNECTIVE TISSUE TUMORS

A) LIPOMA

Definition & origin: A benign tumor of adipose tissue. It is the most common soft tissue tumor.

Sites: It can develop almost anywhere in the human body. Common examples include:

- Subcutaneous tissue, particularly at the region of shoulders, neck, back and buttocks.
- Intermuscular septa
- Mediastinum, mesentery, omentum, retroperitoneal
- Wall of stomach and intestine, and organs as kidney

Gross Picture: A capsulated globular or ovoid, commonly lobulated yellowish soft greasy mass. It is commonly single, but may be multiple (lipomatosis).

Microscopic Picture:

• Classical lipoma consists of lobules composed of mature fat cells (adipocytes) which are large vacuolated cells with flattened eccentric nuclei. The lobules are separated by fibrovascular septa.

• Other uncommon types of lipoma:

- 1-Fibrolipoma: Lipoma associated with abundant fibrous tissue
- 2-Neural fibrolipoma: A special type of fibrolipoma affecting nerves.
- 3-Angiolipoma: Lipoma rich in blood vessels
- 4-Myolipoma: Lipoma associated with smooth muscle proliferation
- 5-Angiomyolipoma: Lipoma rich in muscle and vessels
- 6-Chondroid lipoma: Lipoma containing chondromyxoid foci
- 7-Spindle cell lipoma (pleomorphic lipoma): Lipoma rich in spindle cells
- 8-Lipoblastoma: A tumor of infancy composed of immature fat cells (lipoblasts)
- 9-Myelolipoma: Lipoma containing hematopoietic (bone marrow) cells
- 10-Lipoma with osseous metaplasia

• **Hibernoma:** Consists of a special type of embryonic fat cells (brown fat) which appear smaller than mature fat cells having central nuclei & cytoplasmic vacuoles.

Malignant transformation into liposarcoma is extremely rare if any

B) FIBROMA

Definition & origin: An uncommon benign tumor of fibrous tissue. It may arise in:

- Sites:**
- Dermis and subcutaneous tissue
 - Organs as ovary, wall of GIT and bone

Gross Picture:

A capsulated grayish firm globular or ovoid mass.

Microscopic Picture:

The tumor consists of variable proportions of fibroblasts, collagen and blood vessels. Fibroblasts appear as spindle shaped cells with elongated nuclei showing tapering ends.

Secondary changes as hyalinosis, myxomatous change & calcification may occur.

Malignant transformation into fibrosarcoma is extremely rare if any.

DESMOID TUMOR (FIBROMATOSIS)

Definition: Desmoid tumor belongs to a group of lesions called fibromatosis, characterized by non neoplastic aggressive proliferation of fibrous tissue (aggressive fibromatosis) which infiltrates between neighboring fat cells or striated muscle fibers (benign infiltration). It is classified as a benign lesion since it shows no microscopic features of malignancy and does

Spindle	Fibroblast	3, much long
Cytokeratin	+	+
Tapering end		

Benign infiltration
Fibroblast

* Most Common benign tumor of breast
* Most Common benign tumor ever → Lipoma
UNUSUALLY become malignant

not metastasize However, it is biologically midway between benign and malignant tumors, since it is locally infiltrative & commonly recurs after surgical excision.

- **Pathogenesis:** Unclear.
- **Grossly:** Non-capsulated irregular firm greyish tumor-like mass
- **Microscopically:** Fibroblasts & collagen (similar to fibroma).
- **Examples of fibromatosis:**

- 1- Abdominal desmoid: Arises from the musculo-aponeurotic structures of the anterior abdominal wall in woman during or after pregnancy
- 2-Intra-abdominal fibromatosis: Develops within the pelvis or mesentery
- 3-Extra-abdominal desmoid e.g. in shoulder, pelvic girdle and thigh
- 4-Palmar fibromatosis (Dupuytren's contracture) & plantar fibromatosis.
- 5-Penile fibromatosis
- 6-Infantile and juvenile fibromatosis and myofibromatosis

C) CHONDROMA

Definition & Origin: A benign tumor of cartilage → Chondroblast

Sites:

- Within the interior of bone (enchondroma) most commonly short bones of hands & feet, less commonly at ends of long bones or in flat bones as pelvis, ribs, sternum & scapula.
- Enchondroma is usually solitary & rarely multiple (enchondromatosis, Ollier's disease)
- On the surface of bone (subperiosteal or juxtacortical chondroma).
- Extraskeletal soft tissue chondroma and bronchial chondroma are rare.

Gross Picture:

A globular well demarcated mass, commonly nodular or lobulated. A thin outer capsule may be seen. The tumor is bluish gray and translucent.

Microscopic Picture:

Nodules of cartilage composed of hyaline matrix and cartilage cells residing inside their lacunae. Cartilage cells (chondrocytes) are rounded with vacuolated cytoplasm. Secondary changes particularly myxoid change & calcification are common.

Malignant transformation into chondrosarcoma is rare in solitary chondroma & more common in case of enchondromatosis.

D) OSTEOCHONDROMA

(Exostosis, cancellous osteoma or enchondroma)

Definition, Origin and Sites:

Osteochondroma is a developmental tumor-like abnormality (hamartoma) rather than a true neoplasm. It arises from aberrant lateral growth of the epiphyseal cartilage. They occur in long bones & stop growing after puberty.

Gross Picture: Single or multiple (multiple exostosis, osteochondromatosis). The multiple type is a hereditary autosomal dominant disease. The lesion appears as a mushroom shaped lateral projection composed of a bony stalk & head covered by a cartilaginous cap.

Microscopic Picture: Cancellous bone covered by cartilage.

Malignant transformation → chondrosarcoma. More common in case of multiple exostosis.

E) OSTEOMA

1- OSTEOID OSTEOMA

Definition & Origin:

Benign bone tumor arising in any bone, commonly in the cortex & less commonly within the medullary cavity.

Signet ring appearance
Chondroid inflammation
Lytic change
Mixed changes
Lipoma

Osteoma
Non Caps
osteochondroma
non caps
mushroom like

It is more blessed to give than to receive

Osteoblastoma @ in spine
 ② more than 2cm
 ③ no pain no sclerotic reaction
 + micules Gpc same as osteoid

Sites Any bone, the commonest are femur and tibia.
Gross Picture: The tumor is solitary, less than 2 cm in diameter (commonly < 1 cm). It appears pink, gritty and friable. Osteoid osteomas arising below the periosteum are famous of exciting a tremendous amount of reactive bone that encircles the tumor so that in X-ray films the tumor appears as a radiolucent small lesion (nidus) with dense sclerotic margins.

Microscopic Picture: Trabeculae of osteoid and poorly mineralized woven bone prominently rimmed by osteoblasts. The intervening stroma is loose and richly vascularized.
Complications: Osteoid osteoma causes a characteristic (nocturnal pain) which is dramatically improved by aspirin. Pain is due to excess production of prostaglandin E2.
Remarks: Osteoblastoma is microscopically similar to osteoid osteoma. It differs in the following:
 a) Larger b) painless c) More common in the spine. D) No remarkable periosteal reaction.

2-COMPACT OSTEOMA (Ivory Osteoma): → Practical Jar
Definition, Origin & Sites: Benign tumor arising in membranous bones of the skull.
Gross Picture: A hemispherical, noncapsulated hard ivory-like mass.
Microscopic Picture: concentrically arranged bone lamellae.
Complications: Disfigurement and pressure symptoms e.g. proptosis.

F) MYXOMA
Definition & Origin: A rare benign tumor arising from remnants of primitive mesenchyme.
Sites: The commonest sites are the heart (particularly atrial) and jaw (in relation to teeth).
Gross Picture: A soft gelatinous mass.
Microscopy: Stellate shaped myxoma cells embedded in mucoid matrix.
Complications: Cardiac myxoma may be pedunculated → block the atrio-ventricular valves.
 • Malignant change may occur.

2-BENIGN TUMORS OF MUSCLES (MYOMAS)
A) LEIOMYOMA
Definition & Origin: A benign tumor of smooth muscle.
Sites: It is a common tumor. Sites include:
 • Uterus is the most common site. Leiomyoma is the commonest tumor in females. It occurs during the reproductive period of life and is estrogen-dependent.
 • Wall of esophagus, stomach, intestine, urinary bladder and skin. + erector pili muscle.
Gross Picture (of uterine leiomyoma):
 • Single or multiple.
 • Occurs within the myometrium (intramural, interstitial), but may also occur beneath the serosa (subserous) or immediately beneath the endometrium (submucous).
 • Sharply circumscribed, round and firm.
 • Uncapsulated but may acquire false capsule of compressed surrounding muscles.
 • The cut section is grayish or grayish brown and usually shows a whorly appearance.
Microscopic Picture:
 • Interlacing bundles of smooth muscle cells, which are spindle shaped cells that differ from fibroblasts in having more abundant eosinophilic cytoplasm and rod-shaped nuclei having blunt (non-tapering) ends.
 • Fibrous stroma containing blood vessels. This fibrous stroma may be abundant particularly after the menopause. The tumor may then be called fibromyoma or fibroid.
 • Secondary changes as hyaline, myxoid and cystic changes, ischemic necrosis and calcification are common.

not tumour due to compression in pregnancy
before menopause
after menopause → atrophy
fibromyoma

Leiomyoma Rhabdomyoma
 V.V.V. Common V.V.V. Rare
 rarely V.V.V. Rare V.V.V. Common

Complications: V.V.V. Rare
 • Malignant change into leiomyosarcoma is extremely rare.
 • Uterine myoma may lead to uterine bleeding and infertility.

B) RHABDOMYOMA
Definition & Origin: An extremely rare benign tumor of striated muscles.
Sites: Heart (myocardium) is the commonest site.
Gross Picture: A rounded brownish mass, which may or may not be capsulated.
Microscopic Picture: Striated muscle cells, stroma and vessels.
Complications: Malignant change into rhabdomyosarcoma is common.

3-BENIGN TUMORS OF VESSELS
A) ANGIOMAS
 Benign uncapsulated lesions composed of vascular spaces filled with blood (hemangioma) or lymph (lymphangioma). They are usually detected in early life & represent congenital tumor-like malformations (hamartomas) rather than true neoplasms. They do not change malignant.

A) HEMANGIOMA: Benign tumor / hamartomatous of blood vessels. Two main types:
CAPILLARY HEMANGIOMA
Sites: Capillary hemangioma der 5/10
 • Skin, particularly of face; often since birth (birth mark).
 • Mucous membranes of lip and tongue.
 • Organs as brain & kidney.
Gross: A deep red well defined patch.
Microscopy: Small vascular spaces lined by endothelium containing blood & separated by stroma.
PYOGENIC GRANULOMA: The lesion consists of wide reactive capillary proliferation resembling capillary hemangioma. It occurs in mucous membranes as oral mucosa and skin in response to minor trauma. It is associated with ulceration and secondary infection.

CAVERNOUS HEMANGIOMA
Sites: Cavernous hemangioma
 • Skin, particularly of the face.
 • Mucous membranes of lip & tongue.
 • Enlargement of lip (macrocheilia) or tongue (macroglossia) may occur.
 • Organs as liver, spleen, muscles & bones.
Gross: A purple well defined soft swelling.
Microscopy: Wide vascular spaces lined by endothelium, filled with blood & separated by stroma.

B) LYMPHANGIOMA: A benign tumor / hamartomatous lesion of lymphatic vessels.
Sites:
 • Skin particularly of head, neck and axilla.
 • Mucous membranes e.g. lip and tongue.
 • Viscera as spleen, liver & kidney.
Types, Gross & Microscopic Features:
 ① **Cavernous lymphangioma:** This is the most common type.
Grossly: A grayish pink swelling that may cause enlargement of the tumor site e.g. macrocheilia & macroglossia.
Microscopically: wide vascular channels lined by endothelium, filled with pale eosinophilic lymph & separated by fibrous stroma.
 ② **Cystic lymphangioma (cystic hygroma):**
Grossly: a huge congenital cystic swelling, composed of widely cystic lymphatic channels. It occurs at the side of the neck & may cause troubles in delivery of the baby.
Microscopically: Wider lymphatic channels than cavernous lymphangioma.

B) PERIVASCULAR TUMORS: GLOMUS BODY TUMOR (GLOMANGIOMA)
 An uncommon benign tumor arising from glomus cells surrounding blood vessels.

White Knightblane

BENIGN VASCULAR TUMORS

Capillary Hemangioma



Cavernous Hemangioma



Cystic Hygroma

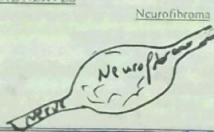
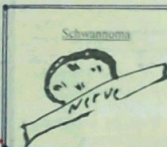


BENIGN TUMORS OF PERIPHERAL NERVES

A) SCHWANNOMA: It arises from schwann cells of any cranial or spinal nerve as a capsulated firm mass located at one side of the nerve. It consists of proliferated schwann cells which have thin palisading nuclei (Antoni type A). The cells may be vacuolated (Antoni type B).

B) NEUROFIBROMA: It is a hamartomatous malformation of nerves. It appears as a fusiform swelling composed of haphazardly arranged nerve fibers and Schwann cells. It may be solitary or multiple (neurofibromatosis syndromes, see systemic pathology).

BENIGN TUMORS OF PERIPHERAL NERVES



INTERMEDIATE (LOCALLY MALIGNANT) TUMORS

1- BASAL CELL CARCINOMA

2- GIANT CELL TUMOR (OSTEOCLASTOMA)

Origin, sites & microscopic appearance: The tumor consists of a mixture of multinucleated osteoclastic giant cells (which proved to be non neoplastic) and neoplastic mononuclear stromal cells of unsettled origin (? osteoblastic or fibroblastic). They can arise from any bone but the most common sites are around the knee joint (distal femur and proximal tibia).

Grossly: An eccentric mass that erodes the subchondral bone. The covering cortical bone becomes markedly thinned (egg shell-like). The tumor tissue is grayish brown and frequently shows cystic degeneration & areas of hemorrhage.

3- CHORDOMA

Origin: It arises from notochordal remnants along the vertebral axis. The most common sites are the sacrococcygeal region and sphenoid-occipital area of the skull.

Grossly: The tumor appears as an infiltrative gelatinous mass.

Microscopically: It consists of cells with vacuolated cytoplasm and vesicular nuclei (physaliferous cells).

Locally malignant

4- ADAMANTINOMA

1- ADAMANTINOMA OF MANDIBLE OR MAXILLA (Ameloblastoma):

- It arises from ameloblasts (tooth epithelium).
- Grossly resembles the appearance of giant cell tumor.
- Microscopically it consists of islands of odontogenic epithelium in a fibrous stroma.

2- ADAMANTINOMA OF LONG BONES:

Tibia is the most common site. The tumor consists of nests of epithelium in a fibrous stroma. The origin of the tumor is unsettled.

Locally malignant

5- CARCINOID TUMOR

- Origin & sites:** It arises from the neuroendocrine cells which are widely distributed in the body e.g. gastric mucosa (most common site), intestinal and appendicular mucosa and any other site such as lung, liver ovary and breast.
- Gross morphology:** Usually defined yellowish grey. Mass 2-5 cm.
- Microscopically:** Small cells showing minimal nuclear atypia, arranged in trabecular, tubular or solid groups. The cells are argyrophilic (positively stained with silver stains).
- Clinical behavior:** is unpredictable. However most appendicular tumors are benign and carcinoids of otherwise sites are mostly locally aggressive but may be malignant metastasizing.
- Carcinoid tumors** may be functioning secreting serotonin and many other peptides. Functioning carcinoid may lead to carcinoid syndrome (see systemic pathology).

Locally malignant

6- CRANIOPHARYNGIOMA

- Origin & site:** Arises from remnants of Rathke's pouch. It is suprasellar (above the pituitary gland).
- Gross:** A suprasellar noncapsulated solid or cystic mass with calcifications.
- Microscopy:** Cystic spaces lined by stratified squamous epithelium and contain an oily fluid in which cholesterol crystals are present.
- Effects:** Compression & destruction of pituitary → hypopituitarism & optic chiasma → visual defects. It may also compress the third ventricle → hydrocephalus.

MALIGNANT EPITHELIAL TUMORS (CARCINOMA)

GENERAL CHARACTERS: See before.

CLASSIFICATION:

I) NON INVASIVE CARCINOMA: CARCINOMA IN SITU: See before

II) INVASIVE CARCINOMA:

A) Carcinomas of surface epithelium include:

- Squamous cell carcinoma.
- Basal cell carcinoma.
- Transitional cell carcinoma.
- Glandular carcinoma mucosal surface.

B) Glandular carcinomas

- Adenocarcinoma.
- Mucoid carcinoma.
- Signet ring cell carcinoma.
- Carcinoma simplex.

C) Carcinomas of serous epithelium

- Choriocarcinoma.

الأورام التي تنشأ من الخلايا الظهارية وتنتشر خارج الغشاء المخاطي أو الجداري.
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Give skin

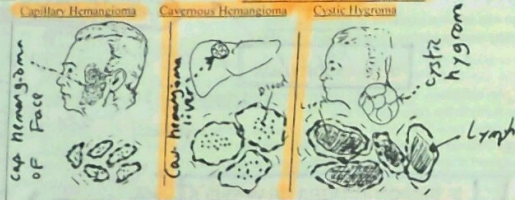
Yasmin

Cell Carcinoma

74
 5. ضامن و 900 طبع
 (الست المستقيمة)

White King before

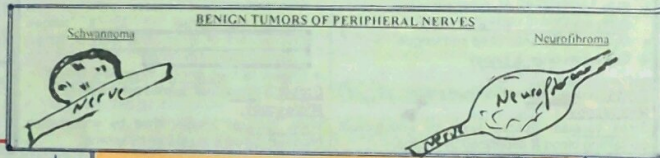
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- Basal cell carcinoma.
- Transitional cell carcinoma.
- Glandular carcinoma (adenocarcinoma & other types) arising from glandular mucosal surfaces e.g. GIT.

B) Glandular carcinoma: Arises from glandular epithelium (endocrine & exocrine glands & glandular mucosa)

- Adenocarcinoma
- Mucoid carcinoma
- Signet ring cell carcinoma
- Carcinoma simplex

C) Carcinomas of special tissues: as hepatocellular carcinoma (liver), choriocarcinoma (placenta) & melanocarcinoma (skin).

Give short account + discuss temple of Local malignant

Basal cell carcinoma

Cell Cholesterol
Local Malignant

1- SQUAMOUS CELL CARCINOMA (Epidermoid Carcinoma)

Definition & Origin: A malignant tumor of stratified squamous epithelium.

Sites:

- Skin
- Mucous membranes lined by stratified squamous epithelium: lip, tongue, oral mucosa, pharynx, larynx, oesophagus, cervix, vagina and anal canal
- Other mucous membranes on top of squamous metaplasia e.g. squamous cell carcinoma can arise in urinary bladder on top of squamous metaplasia due to *bi-hazardal* cystitis.

Predisposing factors:

- a) prolonged exposure to sun.
- b) squamous metaplasia & leukoplakia

Gross Picture: Several patterns:

- Fungating polypoid pattern.
- Ulcerative pattern:
 - Irregular ulcer with raised everted edges
 - Rough necrotic floor.
 - Indurated base.
- Infiltrative pattern.

Microscopic Picture:

The dermis or submucosa is infiltrated by groups of malignant epithelial cells which in well differentiated neoplasms form **cell nests**. These cell nests consist of malignant cells that replicate the organization of the normal epidermis i.e. the periphery of these nests shows basal cell differentiation, followed by prickly cells, then granular cells with the center of the nests showing keratin. In less differentiated neoplasms fewer cell nests are formed & in anaplastic carcinoma, no cell nests may be detected.

Broder's grading of squamous cell carcinoma:

- Grade I: 75-100% of the tumor = cell nests
- Grade II: 50-75% cell nests
- Grade III: 25-50% cell nests
- Grade IV: 0-25% cell nests.

Spread:

- Local spread
- Distant spread (by lymphatics then by blood)

Complication: *Basaloid squamous carcinoma*

2- BASAL CELL CARCINOMA (Rodent Ulcer)

Definition & Origin: A locally malignant tumor arising from basal layer of epidermis of skin

Sites:

The tumor occurs in skin exposed to sun, commonly that of face, particularly above an imaginary line drawn from the angle of the mouth to the lobule of ear, particularly at the inner and outer angles of eyes, side of nose and angle of mouth. Skin of the extensor surface of arms and legs is less commonly affected than face.

Predisposing factors:

- Prolonged exposure to sun. *UV rays*

Gross Picture: The tumor starts as a red papule that gradually enlarges & ulcerates.

- The ulcer is irregular and shows the following features:
 - Raised, rolled in beaded edges
 - Rough floor.
 - Firm base. = indurated

Microscopic Picture:

The dermis is infiltrated by masses of malignant epithelial cells, the peripheral cells are columnar basal cells with **palisade** (parallel) arrangement, while the central cells are polyhedral. There are several variants of basal cell carcinoma e.g. the pigmented type, where tumor masses contain **excessive melanin pigment**.

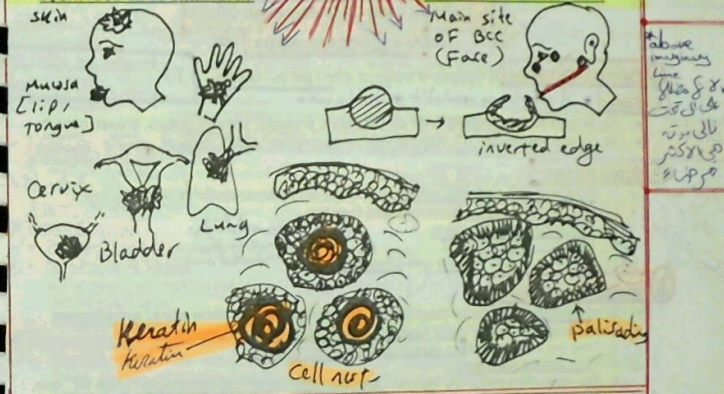
No Keratin Here
No Cell Nest
MCC

Spread:

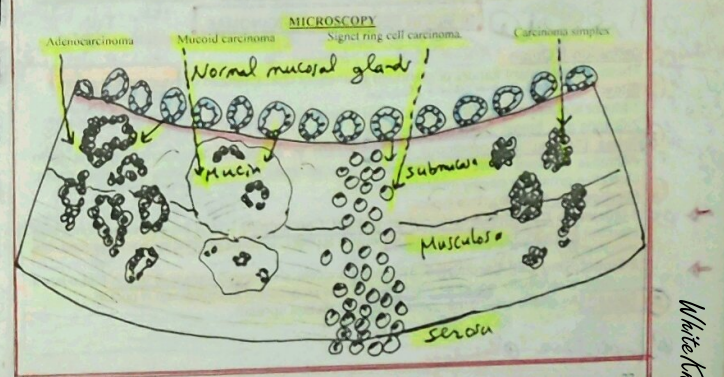
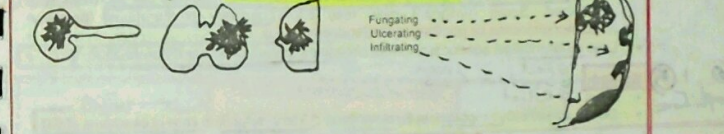
- Local spread only. **No distant spread**

However if basal cell carcinoma changes malignant (basosquamous or squamous cell carcinoma) → distant spread occurs.

Metaplasia & leukoplakia
Sun
Main site of BCC (Face)



CARCINOMAS OF GLANDULAR ORIGIN



well differentiated = resembles normal
Tare + shile + Case + age
Benign no Antidote
Carcinoma Benign Antidote exact treatment

Define cell nest?
Direct to osseous
Direct to lymphatic
Direct to blood
Revise written + oral with your self

Squamous cell carcinoma
Rodent ulcer

White Knight of Cancer

It is more blessed to give than to receive.

4- CARCINOMAS OF GLANDULAR ORIGIN

A) ADENOCARCINOMA = *direct Carcinoma*

Definition & Origin: A malignant tumor of glandular epithelium.

Sites: * *Acetology* * *Colon*

- Endocrine and exocrine glands as pancreas, prostate, salivary glands, breast, ovaries.
- Mucous surfaces as GIT, gall bladder, endometrium, cervix, bronchi.

Gross Picture:

- In endocrine and exocrine glands, the tumor forms an irregular infiltrative growth.
- In mucous surfaces the tumor pattern may be:
 - Fungating polypoid pattern
 - Malignant ulcer type
 - Infiltrative pattern (annular and diffuse subtypes)

Microscopic Picture:

- In well differentiated adenocarcinoma, the malignant cells show acinar arrangement.
- These malignant acini differ from the normal acini in several respects:
 - They are irregular with no definite basement membranes
 - They lumens are irregular
 - The cells show malignant features (pleomorphism, nuclear hyperchromatism, high N/C ratio, mitoses... etc) = *Anaplasia*
 - They exist in abnormal sites (as submucosa, muscularis or serosa) due to infiltration
 - They may be *cystically dilated* (cystadenocarcinoma) if the malignant cell secretions are retained. Some malignant cells may show (papillary proliferations) (papillary adenocarcinoma or papillary cystadenocarcinoma)
- Less differentiated adenocarcinomas show less grades of acinar differentiation

Spread:

- Local
- Distant spread a) By lymphatics b) By blood (late) c) Transcoelomic in case of carcinoma of GIT

B) MUCIN SECRETING CARCINOMAS

Definition & Origin

These are malignant tumors of glandular epithelium characterized by **mucin production**

Sites:

- Mucosal surfaces e.g. GIT, gall bladder & bronchi
- Glands e.g. breast ovaries & pancreas

Gross Picture: Soft gelatinous tumors which in endocrine & exocrine glands form infiltrative masses while in mucosal surfaces may form fungating polypoid mass, ulcerative growth or deeply infiltrative growth.

Microscopic Picture: Two types:

- 1-Mucinous Carcinoma (mucoïd or colloid Carcinoma):** This is an adenocarcinoma with abundant extracellular mucin secretion which appears as pale mucinous pools around the malignant acini.
- 2-Signet Ring Cell Carcinoma:** The malignant cells show intracytoplasmic mucin that pushes the nuclei eccentrically. No acinar differentiation. The prognosis of this neoplasm is poor.

Spread: As adenocarcinoma (local spread & distant spread).

Complications

- ① Perforation
- ② 2nd infection
- ③ distant metastases
- ④ loss function

C) CARCINOMA SIMPLEX

Definition & Origin: A malignant tumor of transitional epithelium. It arises *de novo* or *on top of* villous papilloma. When it arises in the urinary tract it may be called *urothelial carcinoma*.

Sites: Urinary bladder, ureter and renal pelvis. Rarely other sites as ovary

Gross Picture:

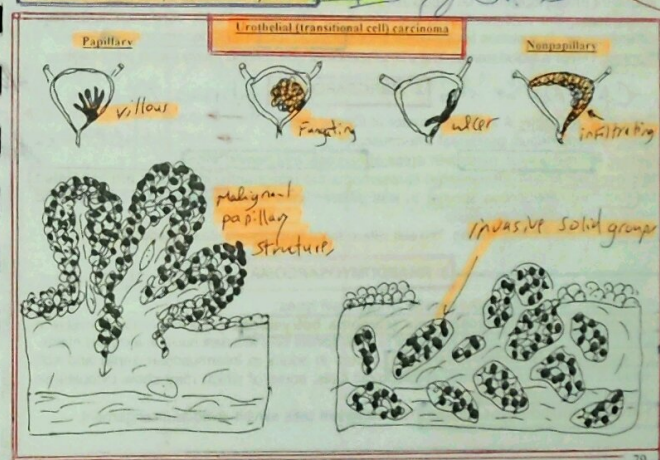
- Papillary Type:** A villous papilliferous growth with broad infiltrating base.
- Non-Papillary Types:**
 - Fungating polypoid mass.
 - Malignant ulcer.
 - Infiltrative pattern.

Microscopic Picture:

- Papillary TCC:** The malignant transitional cells overlie vascular connective tissue cores, usually more than 6 cell layers. Papillary TCC tends to invade less deeply than non-papillary TCC and hence has a better prognosis.
- Nonpapillary TCC:** The malignant transitional cells form solid groups.

Spread:

- Local
- Distant : mainly by lymphatics & late by blood.
- Transluminal implantation may occur.



TCC & TCP → Can't differentiate under microscope if vascular connective tissue more than 6 layers = TCC
Less than 6 layer = TCP

* Kaposi's Sarcoma by human hyper. virus
= AIDS defining illness
Can be Htt
4 clinical typ
rarely cause of death

MALIGNANT MESENCHYMAL TUMORS (SARCOMAS)

GENERAL CHARACTERS: See before (table).

CLASSIFICATION:

- Sarcoma arising from fat cells: Liposarcoma
- Sarcoma arising from fibroblasts: Fibrosarcoma
- Sarcoma arising from striated muscle: Rhabdomyosarcoma
- Sarcoma arising from smooth muscle: Leiomyosarcoma
- Sarcoma arising from vessels: Angiosarcoma & other malignant vascular tumors.
- Sarcoma arising from bone: Osteosarcoma
- Sarcoma arising from cartilage: Chondrosarcoma
- Sarcoma arising from synovial tissue: Synovial sarcoma
- Malignant peripheral nerve sheath tumor (malignant schwannoma)
- Malignant fibrous histiocytoma (unsettled origin)
- Undifferentiated sarcomas: These are sarcomas derived from any of the above cells but without differentiation that points to their origin. They are sometimes designated spindle cell sarcoma, round cell sarcoma, or giant cell sarcoma according to the predominant cell pattern.

CARCINOSARCOMAS:

These are rare tumors composed of a mixture of sarcomatous & carcinomatous elements

1- LIPOSARCOMA

Adipose Tissue

- Definition & Origin:** A malignant tumor of adipose tissue.
- Sites:** Retroperitoneal, mesenteric, mediastinal, intermuscular, subcutaneous.
- Gross Picture:** Large soft mass with foci of necrosis and hemorrhage.
- Microscopic Picture:** In well differentiated liposarcoma, the malignant cells contain abundant intracytoplasmic fat (lipoblastic differentiation). In undifferentiated (pleomorphic) liposarcoma, the malignant cells are extremely pleomorphic with very poor lipoblastic differentiation. Sometimes liposarcoma shows myxoid foci (myxoliposarcoma).
- Spread:** Direct & blood routes. The well differentiated type spreads slowly (better prognosis).

2- FIBROSARCOMA

Fibrous tissue

- Definition & Origin:** A malignant tumor of fibrous tissue.
- Sites:** Subcutaneous, periosteal, intermuscular.
- Gross:** A large grayish mass with areas of necrosis and hemorrhage.
- Microscopy:** In well differentiated fibrosarcoma the malignant spindle cells are separated by abundant collagenous stroma. In less differentiated forms there is little collagen and more marked cellular anaplasia.
- Spread:** Direct & blood routes. The well differentiated type spreads slowly (better prognosis).

3- RHABDOMYOSARCOMA

striated muscle

A malignant tumor of striated muscle. Three main types:

- 1-Embryonal Rhabdomyosarcoma (sarcoma botryoides):** occurs in children; mainly in urinary bladder, vagina & cervix. It consists of small spindle cells with dark nuclei in a myxoid matrix.
- 2-Pleomorphic Rhabdomyosarcoma:** occurs in adults in intermuscular septa and soft tissue. It consists of extremely pleomorphic cells, some of which may show cytoplasmic cross striations (strap cells).
- 3-Alveolar Rhabdomyosarcoma:** The malignant cells exhibit alveolar arrangement.

No Autology in Sarcomas

4- LEIOMYOSARCOMA

Smooth / muscle tumour malignant

- Definition & Origin:** A malignant tumor of smooth muscle. (most common sites: GIT & site)
- Sites:** Most commonly uterus and GIT
- Gross:** Large fleshy mass with areas of hemorrhage and necrosis.
- Microscopy:** Malignant spindle cells with eosinophilic cytoplasm and large dark nuclei. Cytoplasmic actin can be detected by immunohistochemistry.
- Spread:** Direct and blood spread (faster in less differentiated tumors)

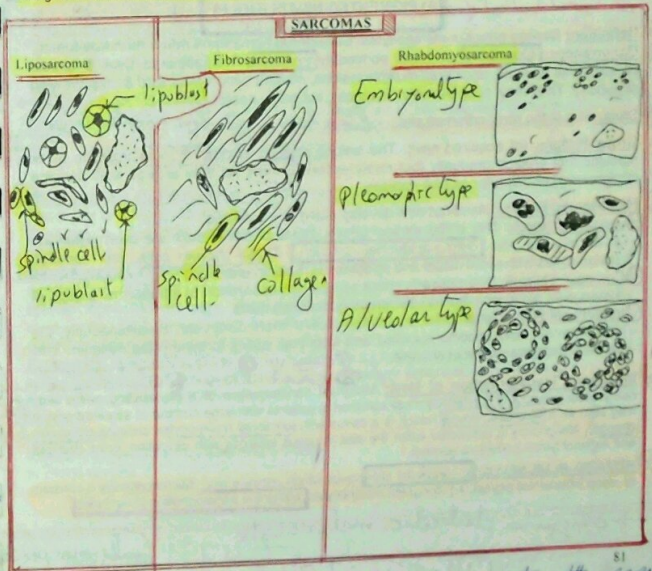
5- MALIGNANT FIBROUS HISTIOCYTOMA

Soft Tissue Sarcoma

- Definition & Origin:** It is the most common soft tissue sarcoma. Origin of the tumor is unsettled.
- Sites:** Soft tissues, rarely bone.
- Gross:** Large fleshy mass with areas of hemorrhage and necrosis.
- Microscopy:** Malignant cells showing fibroblastic, histiocytic, pleomorphic and giant cell patterns in a vascularized collagenous stroma, usually showing inflammatory cells.
- Spread:** Local and blood spread

6- OTHER SARCOMAS

Malignant vascular tumors, osteosarcoma, chondrosarcoma... etc: see systemic pathology



* Lymphangiosarcoma v. Common after Htt surgery
* Angio Sarcoma -> most malignant undifferentiated
* Psammomaepithelioma behave like benign Can be cured - Low grade tumor

White Knight Lane

11/10/20

11

VIP + Juv + slide + Case

Class

MISCELLANEOUS BENIGN & MALIGNANT TUMORS

1- PIGMENTED (MELANOCYTIC) TUMORS

Definition: These are benign & malignant tumors arising from melanocytes.

Sites:

- Skin
- Mucous membranes & mucocutaneous junctions (as conjunctiva, rectum, mouth & vagina)
- Eye as choroid and iris.
- Leptomeninges.

Classification:

- 1-Benign: Pigmented nevus (mole):
 - ▶ A) Congenital types:
 - 1) Giant nevus
 - 2) Blue nevus
 - ▶ B) Acquired types including junctional, intradermal & combined types.
- 2-Malignant: Melanoma.

▶ A) Vertical Type: Nodular melanoma

▶ B) Radial Types:

- Lentigo maligna
- Superficial spreading melanoma
- Acral lentiginous melanoma

A) PIGMENTED NEVUS (MOLE) = Nevus

- 1- **Definition:** Benign tumor of melanocytes. Considered hamartoma rather than true tumor.
- 2- **Occurrence:** Congenital or more commonly acquired. The acquired type is almost present in all persons, usually as multiple lesions, starting during childhood & stop growing at puberty. They may progressively disappear, but some persist.
- 3- **Sites:** Skin is the most common site. Skin + mucous membrane + eye + leptomeninges.

- 4- **Gross Picture:** (of acquired nevi): The lesions start as small (1-2 mm) brown to black macules that enlarge gradually (but rarely exceed 6 mm). As they enlarge they become depigmented and appear as pink papules.

Microscopic Picture: Acquired nevi develop along three phases:

- a) **Junctional Nevus:** This is the earliest phase. Nests of nevus cells are seen within the epidermis, at the dermo-epidermal junction. These nevus cells are rounded melanocytes with ovoid nuclei and cytoplasmic melanin granules.
- b) **Compound Nevus:** This phase is characterized by appearance of intradermal groups of nevus cells along with the intraepidermal (junctional) nests.
- c) **Intradermal Nevus:** over time, the intraepidermal nests disappear. Simultaneously, the dermal nevus cells become spindle and lose their ability to synthesize melanin. This explains depigmentation of old nevi.

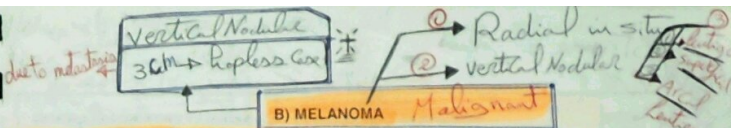
Malignant Transformation of Nevus: Malignant transformation of a pre-existing nevus may rarely occur in adults. It is relatively more common in patients with large number of acquired nevi. It may start as a dysplastic nevus (which is a nevus with junctional melanocytes showing dysplastic change). Malignancy is suspected when the size of nevus enlarges with ulceration, color changes and regional lymph node enlargement.

REMARK: BLUE NEVUS: A congenital skin nevus which appears blue. Microscopically it consists of deep intradermal pigmented elongated melanocytes. Malignant transformation is very rare.

→ origin is dendritic melanocyte

McQ Mole	Melanoma
Benign hamartoma	Malignant

only one place of junction nevi in adult under nail of big toe



Definition & Origin: A malignant tumor of melanocytes. It commonly arises de novo, but nodular melanoma may arise on top of pre-existing acquired or congenital nevi. Malignant transformation of a pre-existing nevus is suspected when the size enlarges with ulceration, color changes and regional lymph node enlargement.

Sites:

- 1-Skin anywhere in the body including head neck, scrotum, palms of hands, soles of feet... etc
- 2-Less common sites include
 - Mucous membranes & mucocutaneous junctions (as conjunctiva, rectum, mouth & vagina)
 - Eye as choroid and iris.
 - Leptomeninges.

Age: Mostly around the age of 40-60 years, but younger and older ages may be affected.

Types (Clark's classification): Two main patterns of growth: Radial and vertical.

Melanomas with Radial Pattern of Growth:

Tumor grows laterally within the epidermis (in situ). Variable dermal infiltration may occur later. Subtypes of radial melanomas include:

- a) **Lentigo Maligna:** 30% invasion within 10-15 + spread along basal epidermis.
 - Appears as a pigmented macule in the face of elderly people + irregular margin
 - Microscopy: Atypical melanocytes, spreading along the basal layer of epidermis.
 - In 30% of cases dermal invasion occurs within 10-15 years.

b) **Superficial Spreading Melanoma:**

- Appears as a slightly raised brown irregular patch in legs or back of the patient.
- Microscopy: Large atypical melanocytes, spreading along all layers of epidermis.
- Dermal invasion occurs in a shorter time than lentigo maligna.

c) **Acral Lentiginous Melanoma:**

- Similar to the two previous types, it represents an in situ malignant melanoma that later becomes invasive. It resembles superficial spreading melanoma with two differences:
- It occurs in hairless skin (palms and soles)
- The neoplastic cells are deeply pigmented

Melanoma with Vertical Pattern of Growth (Nodular Melanoma): 1-3 cm dark brown or pink

The tumor is not preceded by in situ phase. It is an aggressive tumor with poor prognosis. **Grossly:** A raised firm ulcerating nodule, 1-3 cm in diameter, dark brown, but may be pale in color.

Microscopy: Anaplastic melanocytes with cytoplasmic melanin infiltrate the epidermis & dermis. The malignant cells may appear polyhedral forming cohesive groups or appear as spindle noncohesive cells. Rarely the cells do not produce melanin (amelanotic melanoma). Such tumors may be difficult to diagnose except by immunohistochemistry (searching for melanoma antigens e.g. HMB-45).

Prognosis: It depends on the depth of invasion by measuring the vertical extent of tumor below the stratum granulosum (Clark's level). However prognosis is generally poor due to rapid spread of tumor by all routes.

Spread:

- a) Local spread
- b) lymphatic spread to regional lymph nodes
- c) Blood spread.

HMB-45

Define MFH? final common pathway of any soft tissue sarcoma most common soft tissue sarcoma origin of tumors unsettled

White Knightlane

Embryonic Tumors
 @ malig
 @ strict to site
 @ just die of origin
 Origin: In the embryo, each organ is derived from a group of embryonic cells (ectodermal, mesodermal or/and endodermal). After birth, remnants of these cells may exist & continue differentiation for few years. Embryonic tumors arise from these embryonic cell remnants which differ from teratomas in consist of structures derived from the embryonic cells from which the tumor arises (& not from all layers as in teratoma) b) almost always malignant.

Structure:

- Primitive embryonic (undifferentiated) malignant small round cells.
- Some of these primitive cells may differentiate into mature tissues of the same class from which they are derived (e.g. smooth muscle in embryonic tumors derived from mesodermal cells)

Examples:

- 1-Neuroblastoma of adrenal medulla & sympathetic ganglia.
- 2-Retinoblastoma of eye.
- 3-Nephroblastoma of kidney.
- 4-Hepatoblastoma of liver.
- 5-Medulloblastoma of brain.

4- HAMARTOMA

non capsulated

stop at puberty

This is a tumor-like developmental malformation formed of noncapsulated mature tissues of the affected organ, arranged haphazardly. It usually stops growing after puberty. Some are precancerous.

Examples of hamartomas:

- Lung hamartoma (a mixture of cartilage, smooth muscle and bronchial mucosal tissue).
- Kidney hamartoma
- Angiomas (hemangioma and lymphangioma).
- Nevi
- Exostosis (osteochondroma)
- Neurofibromatosis

pulmonary hamartoma

5- LYMPHOMA & LEUKEMIA

MCQ

The reader must refer to systemic pathology for details of these topics.

Lymphomas are a group of primary malignant neoplasms of lymphoid tissue arising from B or T lymphocytes or rarely histiocytes. They most commonly arise in lymph nodes, but may also arise in extranodal sites. Some types are followed by or associated with development of leukemia due to invasion of the blood by large numbers of neoplastic lymphocytes.

Leukemia is a malignant proliferation of one of the leukocyte forming tissue (lymphoid tissue or bone marrow), followed by invasion of blood with large numbers of neoplastic cells. Leukemias may be lymphocytic or myeloid. Lymphocytic leukemias may start as lymphomas. Myeloid leukemias develop primarily in the bone marrow

6- NEUROENDOCRINE TUMORS

VIP

These tumors arise from neuroendocrine (NE) cells. These cells are sometimes known as **APUD** cells (cells capable of **Amine Precursor Uptake and Decarboxylation**). These cells are of several types and exist anywhere in the body. The **secretory function** varies according to the NE cell type. NE tumors include benign, intermediate and malignant forms. However, the behavior of many tumors can not be predicted and may be unrelated to the degree of nuclear atypia.

WHO classification of neuroendocrine tumors

1. Well differentiated endocrine tumors (carcinoid): See before (intermediate tumors)
 2. Well differentiated endocrine carcinomas (malignant carcinoid)
 3. Poorly differentiated endocrine carcinomas as small cell carcinoma (SCC) & large cell carcinoma
 4. Mixed endocrine-exocrine tumors as adenocarcinoma + carcinoid
 5. Mixed neuroendocrine tumors (e.g. gangliocytic paragangliomas)
- Some NE tumors occur as a part of a syndrome called multiple endocrine neoplasia syndrome (MEN syndrome).

No neuroendocrine Benign

prognosis = poor

FACTORS INFLUENCING THE PROGNOSIS OF MALIGNANT TUMORS

1. **Tumor Type:** e.g. melanoma & most sarcomas have poorer prognosis than most carcinomas.
2. **Tumor Site:** e.g. superficial tumors as those arising from skin are diagnosed earlier and treated easier than deeply seated tumors and brain tumors.
3. **Differentiation:** Well differentiated tumors grow slower than less differentiated ones.
4. **Tumor Stage:** The higher the stage the worse is the prognosis. See TNM staging page 65
5. **Immune response against cancer.** See chapter IV p40? Not a killer
6. **Efficiency of treatment:** There are three main methods of treatment of malignant tumors (used separately or in various combinations) including surgery, chemotherapy (anti cancer drugs) and irradiation. The efficiency of treatment affects the prognosis.
7. **Tumor Hormone Receptors:** The growth of some tumors depends partly on hormone stimulation. The cells of such tumors have hormone receptors. Examples include oestrogen receptor positive breast carcinoma and androgen receptor positive prostatic carcinoma. Depriving these tumors from hormone stimulation helps in controlling their growth. Example anti-oestrogen therapy (± oophorectomy) for breast cancer and anti-androgen therapy (± orchidectomy) for prostatic cancer. Thus, a hormone receptor positive tumor is better than a hormone receptor negative tumor.
8. **Growth Fraction (GF):** This is the proportion of cells within the neoplasm entering the cell cycle (i.e. out of G0 phase). The importance of GF is that most anti-neoplastic drugs act on dividing cells; thus tumors with high GF are the most susceptible to anticancer agents & are also the most rapidly growing if left untreated.

AETIOLOGICAL ASPECTS OF NEOPLASIA

Most tumors arise from a single clone of cells (monoclonal) and rarely polyclonal. It is now accepted that changes in the genetic material of the cell is of paramount importance in carcinogenesis. Factors that can produce such genetic damage are called carcinogens. Tumor development is a complex multistep process starting by tumor cell initiation i.e. changing normal cells into abnormal cells (latent tumor cells) through gene abnormalities caused by unknown or known stimuli, followed by tumor cell promotion (transformation of latent cells into tumor cells, that start unlimited division & tumor formation). The requirement of more than one factor for tumor production may explain why cancer develops in some smokers, but not in all smokers.

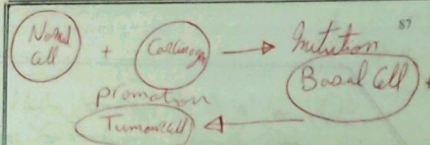
1) THE MOLECULAR BASIS OF CANCER

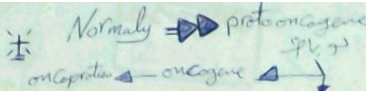
GENETIC PREDISPOSITION OF CANCER:

- Genetic defects may be hereditary e.g. inheritance of RB gene → retinoblastoma, APC gene → colonic cancer & BRCA genes → breast cancer.
- More commonly, genetic defects are acquired, defects causing carcinogenesis involve four classes of normal cell regulatory genes, where gene damage by carcinogens → carcinogenesis (tumorigenesis). These gene classes include growth promoting proto-oncogenes, growth inhibiting tumor suppressor genes (anti-oncogenes) genes that regulate apoptosis & genes that regulate DNA repair.

1- ONCOGENES AND PROTO-GENES

- There are normal cellular genes called **proto-oncogenes** having a potential to transform into cancer-causing **oncogenes**. For this discovery, J Michael Bishop and Harold Varmus received the Nobel Prize in 1989.





③

The Transformation Of Proto-Oncogenes Into Oncogenes occurs by one of three mechanisms:

- 1-Point mutations:** possibly due to exposure to cancer-causing chemicals.
 - 2-Chromosomal translocations:** where during cell divisions, a part of a certain chromosome (with its genes) is relocated into another chromosome leading to gene fusion or change in the sequence of genes, finally resulting in activation and transformation of proto-oncogenes.
 - 3- Gene amplification:** this is reduplication of proto-oncogenes.
- **Oncogenes encode synthesis of proteins called oncoproteins.** These oncoproteins differ from the normal products of proto-oncogenes in that they are devoid of important regulatory elements and that their production in the transformed (neoplastic) cells is not dependent on growth factors or other external signals.

2-TUMOR SUPPRESSOR GENES (ANTI-ONCOGENES)

Cancer may arise not only by activation of growth promoting oncogenes, but also by inactivation of genes that normally suppress cell proliferation (cancer suppressor genes) such as P53 gene. Loss of the P53 gene, inherited aberrations or acquired mutations of the P53 gene are frequently detected in different types of cancer.

3-APOPTOSIS GENES

Some genes as BCL2 prevent apoptosis, thus extending cell survival and in combination with other factors may play an important role in tumorigenesis

4-DNA REPAIR GENES

These genes do not contribute directly to cell growth. However they normally correct errors of DNA that may occur during cell division. Inherited mutations of these genes $\rightarrow$ increased risk of cancer development (genomic instability syndromes)

II) MECHANISM OF NEOPLASTIC TRANSFORMATION

The multistep theory

Carcinogens - acting on cell genes - can lead to tumors through the following steps:

- 1-Initiation:** Induction of certain irreversible changes in the genome of the cells. These initiated cells are not transformed cells and do not have growth autonomy. They just have altered DNA (gene mutation) and are called latent tumor cells.
- 2-Promotion:** Further irritation of latent tumor cells e.g. by some hormones or chemicals (tumor promoters) stimulate the latent cells to undergo autonomous proliferation which is reversible at the early phases.
- 3-Neoplastic transformation:** Abnormal differentiation occurs and the cells undergo continuous purposeless uncontrolled irreversible proliferation.

III) TYPES OF CARCINOGENS

1-CHEMICAL CARCINOGENS: Examples:

- Aromatic hydrocarbons as 3,4 benzpyrene (exist in cigarette smoke) cause cancer lung
- Aromatic amines as B naphthylamine : cause cancer bladder
- Bacterial metabolites (as nitrosamines): cause cancer stomach
- Azo dyes as scarlet red (containing dimethyl amino-azobenzene) cause hepatic cancer.
- Asbestos: cause mesothelioma.
- Allatoxins (produced by Aspergillus flavus fungus) cause hepatic carcinoma
- Vinyl chloride cause hepatic angiosarcoma
- Alkylating agents (as mustard gas) cause nasal, laryngeal and lung cancer
- Arsenic (skin cancer), nickel and chromium (lung cancer)

2-PHYSICAL CARCINOGENS:

- Prolonged exposure to ultraviolet rays (sun) can cause skin malignancy (basal cell carcinoma, Squamous cell carcinoma, melanoma).
- Ionizing radiations cause leukemia, osteosarcoma, skin malignancy and lung cancer.

3-VIRUSES:

- Some viruses are oncogenic. They are either DNA or RNA viruses. Infection of human cells with these viruses can alter the genetic material.
- Examples of DNA viruses include hepatitis C (liver cancer), Epstein Barr virus (nasopharyngeal carcinoma and Burkitt's lymphoma), human papilloma virus (carcinoma of cervix).
 - Example of RNA viruses is human T cell Leukemia virus-1 (T cell lymphoma & leukemia)

4-HORMONES:

- They cannot cause tumor initiation but may act as promoters. Examples include
- Oestrogen:** High levels of oestrogen (as in non-ovulating adults & in cases of granulosa cell tumor of the ovary) can promote endometrial carcinoma & mammary carcinoma.
 - Diethyl stilbesterol (DES):** Administration of DES in a pregnant lady can promote vaginal adenocarcinoma (clear cell type) in her baby (if female) later on in life.
 - Androgens:** Androgen in high levels can promote prostatic carcinoma.
 - Role of contraceptive pills:** in cancer breast is questionable. However they can lead to benign tumors of liver (hepatic adenoma)

IV) CHRONIC DISEASE PREDISPOSITION (PRECANCEROUS LESIONS)

V.I.P.

Some chronic diseases may lead to a precancerous lesion (a non-malignant lesion that is liable to undergo malignant transformation). Examples include:

1-Chronic Inflammatory Diseases as:

- Bilharziasis of the urinary bladder.
- Ulcerative colitis
- Atrophic gastritis
- Radiodermatitis
- Tertiary syphilis of tongue
- Lupus vulgaris (cutaneous T.B.)

2-Gall stones and urinary stones

3-Hyperplastic and metaplastic lesions as leukoplakia, endometrial hyperplasia, mammary hyperplasia.

4-Some Benign Tumors e.g. villous bladder papilloma & GIT adenomatous polyps.

5-Others as liver cirrhosis, varicose ulcers, Paget's disease of bone, undescended testis.

V.I.P.

V) CO-CARCINOGENS (Helping Factors)

- 1. Aging:** increases the risk of some types of cancer (prolonged exposure to carcinogens), e.g. prostatic cancer is almost present in every male above the age of 100 years.
- 2. Sex:** Males are generally more susceptible to cancer, however some carcinomas predominate in females as breast carcinoma (very rare in males) & thyroid carcinoma.
- 3. Diet:** Diet rich in fat is related to colorectal cancer, while smoked fish is related to gastric cancer.
- 4. Environmental Factors:** e.g. air pollution (lung cancer), farmers (skin cancer due to prolonged exposure to sun).
- 5. Trauma:** It may be related to some types of cancer as osteosarcoma.
- 6. Histocompatibility type & blood group:** e.g. gastric carcinoma is more common in blood group A persons.

Liver cirrhosis $\Rightarrow$ no estrogen Metabol. in $\rightarrow$ Estrogen $\rightarrow$ Carcinogenesis

Write tonight

MCQ

SPONTANEOUS TUMOR REGRESSION

- Rarely cancer may suddenly regress spontaneously (without treatment) & permanently (without recurrence). The mechanism is not known; may be immunological or hormonal.
- Examples of such tumors include malignant melanoma, neuroblastoma, choriocarcinoma & clear cell type of renal cell carcinoma. There are also rare known examples of regression of metastases after removal of the primary e.g. in cases of malignant melanoma or choriocarcinoma metastases. Another fascinating example of tumor regression is maturation of malignant cells into benign tumor cells or into normal non neoplastic cells as in case of neuroblastoma and teratoma of the testis

LABORATORY DIAGNOSIS OF NEOPLASIA

1-Biopsy

2-Fine-needle aspiration e.g. from breast, thyroid or LN tumor

3-Cytological examination: Fluids such as ascites, pleural effusions, CSF and urine may contain detached malignant cells from anatomically-related tumors

4-DNA Flow Cytometry: It shows abnormal DNA pattern of tumor

5-Tumor Markers: V.I.P (o,p,p)

These are tumor-derived or associated molecules. They may be secreted in the blood (serum tumor markers) and can be detected within the tumor cells (tissue tumor markers).

a) Serum Tumor markers detected within the blood:

Assessment of the level of these markers helps in diagnosis & follow up of tumors e.g.:

① Carcinoembryonic antigen (CEA) in cancer colon, stomach, pancreas & breast.

② Alphafetoprotein (AFP) in hepatic cancer and germ cell tumors.

③ Prostatic specific antigen (PSA) & prostatic acid phosphatase in cancer prostate

④ CA125 (adenocarcinoma particularly ovarian)

⑤ CA 19-9 (adenocarcinoma particularly colonic).

• Example: Colonic cancer is surgically treated by colectomy. If after colectomy CA19-9 was normal, but on follow up it progressively increased this would be most likely denote development of colonic cancer metastases.

b) Tissue Markers localized within tumor cells: These can be detected by a special technique called IMMUNOHISTOCHEMISTRY. According to their type they may be detected in the cell membrane, cytoplasm or nuclei. Common examples include:

• Epithelial markers: Cytokeratins (CK) (low and high molecular weight types) & epithelial membrane antigen (EMA). Positive in epithelial tumors as carcinoma

• Mesenchymal markers as Vimentin → mesenchymal tumors /sarcoma.

• Leukocyte markers such as:

- Leukocyte common antigen (LCA) positive in lymphomas & other leukocytic lesions.

- CD 20: Positive in B lymphocytes

- CD 3: Positive in T lymphocytes

• Endothelial markers as Factor VIII-associated antigen (F VIII) & CD 34

• Mesothelial markers as Calretinin

• Neural markers as S-100 protein. Also positive in many other tumors as, melanoma & cartilaginous tumors

• Melanocytic markers as HMB 45 & melan A → melanoma.

• Muscle markers as desmin & smooth muscle actin (SMA)

• Neuroglial markers as glial fibrillary acid protein (GFAP)

• Neuroendocrine markers as neuron specific enolase (NSE), chromogranin and synaptophysin Estrogen receptors (ER) & progesterone receptors (PR) → breast carcinoma.

• Thyroid markers: thyroglobulin & TTF1 (thyroid transcription factor 1)

- Other markers as PSA: → prostatic carcinoma, CEA → GIT carcinoma (& many others). AFP → hepatic carcinoma and some germ cell tumors, estrogen receptors (ER) & progesterone receptors (PR), both are commonly positive in breast cancer (& few other tumors), c-Kit (for gastrointestinal stromal tumors and germ cell tumors)
- Proliferation markers as Ki67 detect rate of cell proliferation
- C-erb B2 (Her2): This marker is related to high metastatic potential

Significance of immunohistochemistry:

- Diagnostic:** The cellular origin of undifferentiated tumors is difficult to recognize. Tumor markers will be greatly helpful.

Examples

- An undifferentiated malignant tumor positive for CK & negative for vimentin, LCA, CD34, HMB45... etc will be diagnosed as undifferentiated carcinoma
- If a brain tumor is questioned for whether primary or metastatic and proved positive for GFAP, what do you think? → Primary origin. What if in a female it was negative for GFAP and positive for CK & ER. What do you think? → Metastatic carcinoma from breast
- Prognostic & therapeutic:** e.g. breast cancer positive for ER & PR and negative for Her 2 is much better than breast cancer negative for ER & PR and positive for Her2. The former is treated by antiestrogen drugs (as tamoxifen) and the later is treated by chemotherapeutic drugs mainly herceptin

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① fibrinogen → fibrin = clotting
 ② platelets + fibrin ⇒ thrombus ⇒ clott + platelets
 VIP + sub + T + G → 2. THROMBOSIS ⇒ during life
 ⇒ inside CVS

DEFINITION: A thrombus is a solid compact mass formed inside the cardiovascular system during life from circulating blood constituents. It primarily consists of platelets with a variable amount of clotted blood. The clot component consists of fibrin entangling blood cells.

AETIOLOGY: Endothelial injury, Stasis & turbulence of blood flow, Change blood composition, Hyperviscosity of blood

1) ENDOTHELIAL INJURY:
 Causes of endothelial injury include: = *avascular*
 • Atherosclerosis (تصلب الشرايين)
 • Traumatic injury of arteries and veins
 • Inflammations (phlebitis, arteritis, endocarditis)

Endothelial injury is an important cause of thrombosis due to:
 • Exposure of subendothelial collagen, to which platelets can stick firmly.
 • Release of thrombotic factors as factor VIII. Anti-thrombotic factors are also released.

2) ALTERATION IN THE BLOOD FLOW (STASIS AND TURBULENCE):
STASIS (SLOWING): Stasis → deviation of platelets from the axial blood stream → contact with the endothelium → enhancement of thrombosis. Causes of stasis include:
 • Venous thrombosis due to heart failure
 • Varicose veins
 • Left atrial stasis in case of mitral stenosis
 • Acute inflammation
 • Hyperviscosity states due to changes in blood composition (see below)

TURBULENCE OF BLOOD (DISORDERS OF BLOOD STREAM) = stasis + eddy current
 • Definition: Turbulence is deviation & distortion of the blood stream (eddy current) → the blood stream abnormally hits the vascular or cardiac lining → deviation of platelets + endothelial damage. Turbulence is usually associated with stasis.
 • Examples of turbulence include:
 o Inside arterial aneurysms → Localized dilatation of arteries
 o Inside atria in case of atrial fibrillation
 o Vascular compression from the outside (e.g. by tumors)

3) CHANGE IN BLOOD COMPOSITION
 • Increased red blood cells in case of polycythemia (تصلب الدم) → Tumors
 • Increased white blood cells in case of leukemia
 • Loss of plasma in case of dehydration (e.g. after surgery) or burns
 • Increased fibrinogen (during pregnancy)
 • Macrogllobulinemia

4) HYPERCOAGULABILITY OF BLOOD: = Hypercoagulability
 It is alteration in clotting mechanisms predisposing to thrombosis. The causes include:
 • Inherited lack of natural anticoagulants: antithrombin III, protein C or protein S.
 • Acquired states e.g. in cases of oral contraceptives, hyperlipemia, nephrotic syndrome, severe trauma, surgery, disseminated cancer, late in pregnancy, heart failure, & severe burns. Mechanism of hypercoagulability is not clear.

MECHANISM (MODE OF FORMATION) OF THROMBOUS:
 The following events occur if there is endothelial injury.
 1) Exposure of subendothelial collagen & release of endothelial thrombotic factors. Antithrombotic factors are also released.

Thrombus & Condition = definition
 • Solid compact mass
 • Cardiovascular system
 • Platelet + clot of fibrin entangling blood
 * VECOW *
 • Venous thrombus
 • Arterial thrombus
 • Cardiac thrombus
 • Blood flow
 • Platelet + fibrin

2) Adhesion of the platelets to the exposed collagen. This is mediated by von Willebrand factor (factor VIII), which acts as a bridge between platelet surface receptors & collagen. Factor VIII is produced by the endothelial cells.

3) Platelet release reaction: Various platelet-derived factors are released (serotonin, ADP & others). ADP → platelet aggregation (which may be reversible). However, with progressive increases of ADP + the secretion of thromboxane A2 (TXA2) from the platelets → platelet contraction → irreversible mass of aggregated platelets (thrombus).

4) Platelet Factor 3 is activated and exposed at the surface of aggregated platelets. This PF-3 is involved in the process of formation of thrombin from prothrombin.

5) Thrombin leads to transformation of fibrinogen into fibrin. The end result is a platelet/fibrin plug (thrombus).

CLASSIFICATION OF THROMBI:

1) According To Thrombus Color:
 As previously shown, a thrombus consists of a platelet mass and fibrin clot. According to the relative amounts of platelets and clot, thrombi may be:
 a) Pale thrombi: They predominantly consist of platelets with little fibrin.
 b) Red thrombi: They consist predominantly of clot elements with little platelets. Red thrombi mainly occur in veins in cases of stasis.
 c) Mixed thrombi: are more common in arteries & heart but can also develop in veins. They consist of alternating lamellae of platelets (called lines of Zahn) and fibrin. There are two forms of mixed thrombi:
 • Coralline thrombus: The alternating platelet and fibrin lamellae are perpendicular to the initial pale platelet thrombus. The thrombus resembles coral.
 • Laminated thrombus inside aneurysms: It consists of platelet and fibrin lamellae parallel to the wall of aneurysm.

2) According To Whether Occlusive Or Not:
 a) Non-occlusive (mural) thrombi occur in capacious sites as aorta and heart.
 b) Occlusive thrombi: The vascular lumen is occluded. This is the commonest form.
 • It most commonly starts as an occlusive thrombus in veins of the lower limb.
 • Clotting occurs in the proximal stagnant blood column & stops opposite the next venous tributary (where the blood is moving & stagnation is absent).
 • Platelets adhere to the terminal margin of the clot → another occluding thrombus → further proximal stagnation → clotting which stops opposite the next venous tributary.
 • The process may be repeated several times & in this way the thrombus (& clots) propagate towards the heart.

3) According To Presence Or Absence Of Bacteria:
 a) Sterile thrombi containing no bacteria.
 b) Infected (septic) thrombi as in cases of septic thrombophlebitis & septic vegetations in acute bacterial endocarditis.

4) According To The Site Of Thrombosis:
 a) Arterial Thrombi: common in cases of:
 • Atherosclerosis
 • Aneurysms
 • Arteritis
 b) Cardiac Thrombi:
 • Valvular thrombi (Vegetations): These are small thrombi developing on inflamed valves (valvular endocarditis) e.g. rheumatic endocarditis or bacterial endocarditis.
 • Atrial thrombi in case of atrial fibrillation
 • Ventricular mural thrombi develop opposite myocardial infarction

* Localized dilatation of vein = Varicose vein
 * Localized dilatation of artery = aneurysm
 Arterial thrombi (oral) = ...

* Lines of Zahn = fossil platelets = alternating lamellae of platelets & fibrin

White Knightlane

It is more blessed to give than to receive.

VIP

c) **Venous Thrombosis**: Common due to slower venous circulation & because veins are thin walled → easier injury by trauma than arteries. Two main types of venous thrombosis:

• **Phlebothrombosis**:

Definition: This is thrombosis in noninflamed veins.

Effects: Congestion & oedema. Pulmonary embolism or propagating thrombus may also occur

Examples:

- Thrombosis in varicose veins due to stasis.
- Thrombosis of pelvic & leg veins after labour or surgery due to:

- o Increased platelets
- o Bed recumbence → compression of calf veins against the bed mattress
- o Traumatic surgical injury.

- Thrombosis of calf veins in cases of heart failure due to

- o Slow circulation
- o Bed recumbence.

• **Thrombophlebitis**:

Definition: This is thrombosis in inflamed veins.

Types:

- **Aseptic (sterile) thrombophlebitis** not caused by bacteria. Example: irradiation

- **Septic thrombophlebitis**: Inflammation is caused by pyogenic bacteria → septic thrombi → fragmentation → septic emboli → pyemia. Examples:

- o Pelvic veins in case of puerperal sepsis.
- o Appendicular vein in case of acute suppurative appendicitis.
- o Veins in the vicinity of abscess, cellulitis or any other septic infection.

d) **Capillary Thrombosis**: Rare. May occur in cases of frost bite.

5) **FATE AND COMPLICATION OF THROMBI**: 7 Karto V.I.P

1) **SEPTIC THROMBI**: → Fragmentation by proteolytic enzymes released due to infection → septic emboli that circulate in the blood → pyemic abscesses (pyemia)

2) **ASEPTIC THROMBI**:

a) Lysis of early small thrombi may occur by fibrinolysis.

b) **Organization (fibrosis)** due to invasion of the thrombus by granulation tissue derived from the subendothelial zone

c) **Recanalization**: The granulation tissue that invades the thrombus consists of fibroblasts and capillaries. Capillaries may form wide anastomosing channels that cross between the two ends of the thrombus to establish some vascular continuity.

* d) **Calcification of venous thrombi (phlebolith)**

e) Incorporation of arterial thrombi into atheroma.

f) **Embolization**: The effects of aseptic emboli depend on the efficiency of collaterals:

- With poor collaterals → ischemic necrosis (infarction or gangrene) = bad anastomosis
- With good collaterals → no major effects = good anastomosis

g) Occluding thrombi may lead to:

- Ischemia (if arterial)
- Congestion & oedema (if venous)
- Propagation in some cases.

Remark: **CLOTTING**: not disease while thrombosis disease

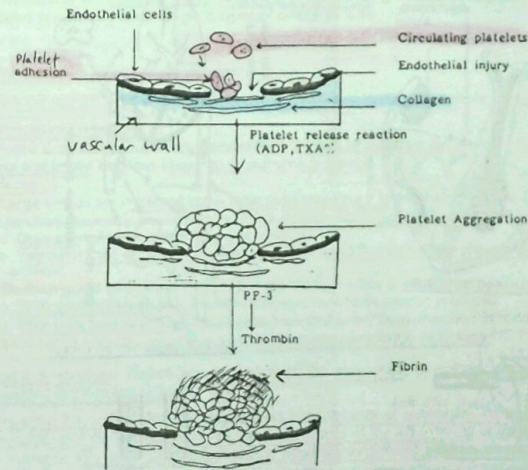
Clotting is defined as transformation of fibrinogen into fibrin. Clotting occurs in cases of:

- 1- Outside the cardiovascular system due to hemorrhage
- 2- Inside the cardiovascular system during life as a part of the process of thrombosis
- 3- Inside the cardiovascular system after death (post-mortem clot).

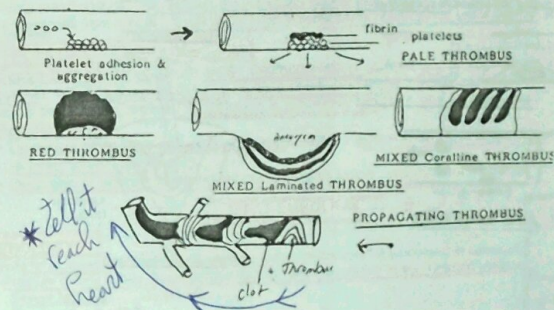
+ emboli are dangerous
+ thrombus is not dangerous

Thrombus only in life
emboli are dangerous
thrombus is not dangerous

THROMBOSIS Mechanism

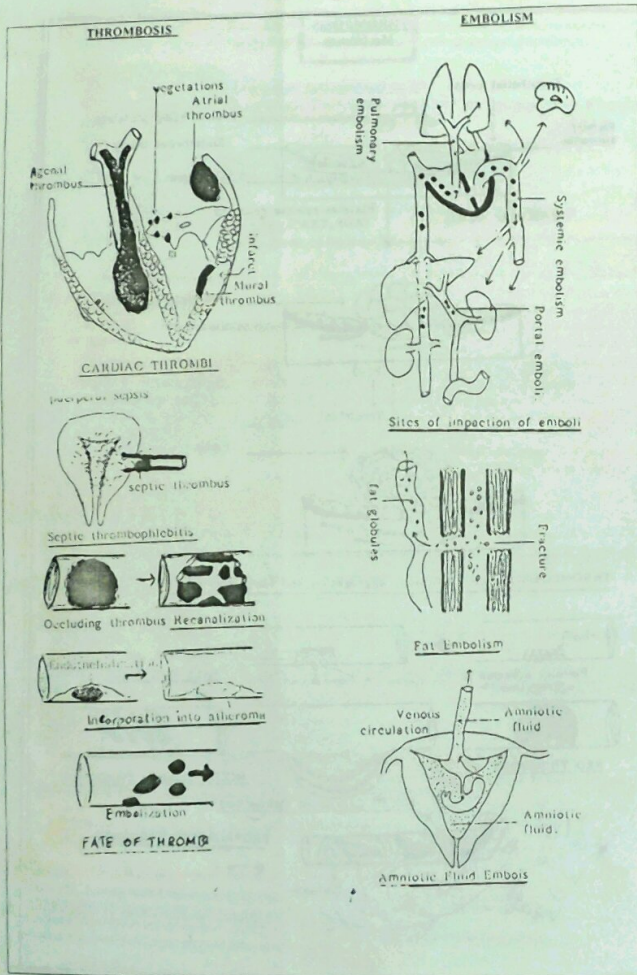


THROMBOSIS: Platelet adhesion, aggregation and fibrin formation.



* tell it reach heart

White Knight Lane



fat embolism @ thromboembolism
 Amniotic " " " " " "
 Gas (air) " " " " " "
 Tumour " " " " " "

3- EMBOLISM

7
 VIP+ Case

An embolus is an insoluble mass circulating in the blood. Embolism is impaction of the embolus in a blood vessel. Origin & types of emboli include:

A) THROMBOEMBOLISM

AETIOLOGY: Fragmented or detached thrombi.

SITES OF IMPACTION of the emboli may be pulmonary, portal, systemic or paradoxical:

1) Pulmonary Embolism:

Source & course: Emboli are derived from thrombi of systemic veins, reach the venae cava and finally become impacted in pulmonary arteries

Effects:

- 1-Large emboli** are impacted in the main pulmonary trunk or the main pulmonary branches (massive pulmonary embolism) → sudden death (acute heart failure). Mechanism:
 - Obstruction of blood outflow from right ventricle
 - Vasoconstriction of pulmonary arterioles due to serotonin released from platelets of the large embolus.
- 2-Medium-sized emboli** are impacted in the medium-sized & small branches:
 - With good collateral flow (bronchial artery), no effects may be produced
 - With poor collateral flow (inadequate bronchial artery flow) infarction develops.
- 3-Very small emboli** may have no effect or cause paradoxical embolism.

2) Portal Embolism

Emboli are derived from the mesenteric or splenic veins and are impacted in the portal radicles.

3) Systemic Embolism:

Emboli are derived from thrombi of pulmonary veins, left atria, vegetations of the left sided valves, mural thrombus of the left ventricle or aortic thrombi → systemic arterial circulation & become impacted in different sites as cerebral, renal, splenic & hepatic arteries. Their effects are described below (see effects of thrombo-embolism).

4) Paradoxical Embolism:

Emboli circulating in the systemic veins may not cause pulmonary embolism and instead lead to systemic embolism by one of two mechanisms:
 1-Very small emboli may by-pass the pulmonary capillaries & reach left side of heart. ★
 2-Emboli pass from right to left side of the heart in some cases of congenital septal defects. ★

EFFECTS OF THROMBOEMBOLISM:

1)**Septic Emboli** derived from septic thrombophlebitis or from septic vegetations cause pyemia, which is characterized by multiple small abscesses, usually peripherally located within the affected organ. The condition is commonly fatal.

2) Aseptic Emboli:

- Occlusion of arteries with poor collaterals leads to ischemic damage of the tissue → infarction or gangrene.
- Occlusion of arteries with efficient collateral circulation: insignificant effects.

B) FAT EMBOLISM

AETIOLOGY:

Minute fat globules reach the pulmonary circulation (pulmonary fat embolism) in cases of:
 • Fracture of long bones. Bone marrow fat may reach circulation through injured vessels.
 • Severe fatty liver
 • Skin burns

* bone = oil
 * Paradoxical embolism

Comparison * Pyemia
 → pus in sac e.g. placenta in Amniotic fluid
 → septic emboli in blood

* old bone marrow yellow has fat
 * young marrow red
 * White Knightmare

Supersensitivity $\rightarrow$ $\frac{1}{2}$ of 1st & 2nd *
Corticosteroids $\rightarrow$ 1st & 2nd *

C) AMNIOTIC FLUID EMBOLISM

Incidence: A rare condition occurring in one every 50,000 to 80,000 deliveries.

Pathogenesis is unclear, but infusion of amniotic fluid into the maternal circulation may be induced by vigorous uterine contractions.

Effects: It is a major cause of maternal mortality due to:

- The amniotic fluid contains vasoactive substances as prostaglandins → pulmonary vasoconstriction
- The amniotic fluid contains thrombogenic factors → intravascular coagulation (disseminated intravascular coagulopathy, DIC). Fibrin plugs occlude several small vessels.

D) GAS (AIR) EMBOLISM

a) Single embolism: as in case of injury of a neck vein → suction of atmospheric air during inspiration → air bubbles reach the superior vena cava → right ventricle frothing → serious impairment of cardiac action.

b) **Multiple embolism:** It occurs in Caisson disease or decompression sickness.

In divers the high atmospheric pressure leads to dissolution of high concentrations of atmospheric gases in their blood. If divers are decompressed too quickly, these gases come out in the circulation in the form of bubbles. Occlusion of several vessels including the cerebral vessels leads to serious ischemic effects.

E) TUMOR EMBOLI

See hematogenous spread of malignant tumors.

F) PARASITIC and BACTERIAL EMBOLI

Such as bilharzia ova and clumps of bacteria.

G) FOREIGN BODY EMBOLI

These are rare e.g. crushed tablets injected intravenously in drug addicts

4- ISCHAEMIA

This is reduction of arterial blood supply to a tissue. Two types

A) ACUTE ISCHEMIA (Sudden Complete Arterial Occlusion)

Causes:

- 1) Thrombosis (particularly on top of atherosclerosis)
- 2) Embolism Embolism & thrombosis are the most 2 common causes of acute ischemia
- 3) Surgical ligation of an artery
- 4) Strangulation of vessels as those of intestine in case of strangulated intestinal obstruction
↳ strangulated hernia, intussusception and volvulus ★
- 5) Twisting of vessels as those of ovary and testis ♀
- 6) Severe arterial spasm as in a) Raynaud's disease A rare disease usually affecting young women, characterized by spasmodic attacks of small arteries & arterioles in response to cold
→ ischemia b) Ergot poisoning ★
- 7) Buerger's disease inflammatory occlusion of vessels in heavy smoking middle-aged males.
- 8) Frost bite Injury & occlusion of capillaries and arterioles in severe cold.
- 9) Severe arterial compression as in cases of :
 - tight tourniquet *Arteria femoralis claudicans*
 - Over bone prominences in cases of prolonged recumbence (see bed sores).

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Acute = Sudden complete
Chronic = Gradual incomplete } Distal

10) Extensive venous obstruction (as in mesenteric venous thrombosis) may → marked engorgement of venous capillaries → this impedes the arterial blood flow → ischemia.

Effects: Effects of arterial occlusion depend on the efficiency of collaterals

- 1) Efficient collaterals → minimal or significant effects.
- 2) Poor collaterals → ischemic necrosis (infarction or gangrene).

B) CHRONIC ISCHEMIA (Gradual Incomplete Arterial Occlusion)

Causes:

- 1) Atherosclerosis ✓✓✓
- 2) Endarteritis as in syphilis ★
- 3) Arterial compression e.g. by tumors. ★

Effects:

- 2) With poor collaterals, the following effects occur:
- Pain on exercise e.g. angina pectoris (cardiac pain) and intermittent claudications (lower limb muscle pains)
 - Patchy cell injury → patchy fibrosis of the affected tissue e.g. myocardial fibrosis in cases of coronary atherosclerosis & renal fibrosis in case of atherosclerosis of renal artery.

Occlusion of artery with good collateral → No effect

Occlusion of artery with poor collateral → Necrosis with no putrefaction = infarction

Occlusion of artery with poor collateral → Necrosis followed by putrefaction = gangrene

Burger disease

Ischaemia ← the angiotensin, کان
و قهوه و عسل و دیگره ایله
و قهوه مرانه قهوه به مجاری ما
و قهوه قهوه قهوه

White Knight Love

INFARCTION

DEFINITION:

An infarct is an area of ischemic necrosis due to sudden ischemia. The type of necrosis is coagulative except in CNS infarction, which is liquefactive.

AETIOLOGY:

- 1) Arterial occlusion by thrombus or embolus represents about 99% of cases.
- 2) Extensive venous obstruction may rarely lead to ischemia (see above).

TYPES OF INFARCTS:

1) Infarcts Due to Arterial Occlusion:

- The occluded artery has poor collaterals, therefore immediately after occlusion no blood reaches the area which becomes an infarct.
- After 24 hours blood collects in the area following dilatation of the poor arterial collaterals. Thus the infarct appears red.
- After 36 hours the necrotic cells within the infarct become swollen. The results are:
 - a) In solid organs as heart & kidney, the blood cells within the ischemic area are squeezed outside the area; thus the infarct appears pale & is called pale or anemic infarction.
 - b) In loose richly vascularized tissues as lung, there is excess blood in the ischemic area which is not squeezed out - red hemorrhagic infarct.

2) Infarcts Due to Venous Occlusion:

- These are red hemorrhagic infarcts due to venous occlusion (with or without arterial occlusion).
- Examples:
 - a) Infarcts of intestine due in cases of strangulated intestinal obstruction.
 - b) Infarcts of ovary and testis due to twisting of their vessels.
 - c) Brain infarction in case of jugular vein thrombosis.

GENERAL PATHOLOGICAL FEATURES OF INFARCTS:

Gross Features:

- The infarct is usually pyramidal or wedge-shaped with its apex at the site of vascular occlusion and its base at surface of the organ. This is due to the fan-shaped distribution of arteries (arteries with poor collaterals).
- When the infarct base is a serosal surface (pleura, pericardium or peritoneum), it shows fibrinous exudate (due to fibrinous inflammation).
- Margins of the infarct are hyperemic due to inflammation.
- Early the infarct is swollen, but later it becomes contracted due to healing.
- Infarcts may be pale or hemorrhagic (see before).

Microscopic Features:

- Infarcts of all organs except CNS consist of coagulative necrosis. The necrotic cells retain their structural outlines for sometime but later become structureless. CNS infarcts are structureless from the start (liquefactive necrosis).
- The margins of the infarct show dilated capillaries and some inflammatory cells.
- The rest of the organ appears normal except in case of lung infarction where the lung shows picture of chronic venous congestion (see below).

Fate: Healing. Dystrophic calcification may occur.

General Changes: Leukocytosis and fever are common.

EXAMPLES OF INFARCTION:

1) Lung Infarction:

- Aetiology: The lung has a double blood supply, therefore infarction does not occur unless both pulmonary and bronchial arteries are affected.
- Pulmonary occlusion is by thrombosis or embolism.

- Inefficient bronchial blood supply occurs in cases of lung congestion. Lung congestion is caused either by mitral stenosis or left ventricular failure. These diseases that cause lung congestion simultaneously lead to low cardiac output → inefficient bronchial blood flow.

Gross picture: A pyramidal subpleural red infarct, the pleural covering shows fibrinous exudate. Early the infarct is swollen. Later healing occurs.

Microscopy:

- a) Ghosts of necrotic alveolar walls. Alveolar lumens are filled with blood (hemorrhagic infarct).
- b) The margins are inflamed.
- c) The adjacent lung tissue shows picture of chronic venous congestion.

Clinical Features: Chest pain and hemoptysis. Due to pleural exudation.

2) Intestinal Infarction:

It may be either due to occlusion of mesenteric arteries by thrombus or emboli or due to intestinal strangulation. The importance of intestinal infarction is that it progresses to gangrene due to putrefaction by intestinal bacteria. Mortality is high due to intestinal obstruction and marked toxemia.

3) Cerebral Infarction:

Aetiology:

- a) Thrombosis or embolism affecting cerebral arteries.
- b) Jugular vein thrombosis.
- c) Severe shock.

Gross Features:

- The site of infarct depends on the affected vessel.
- The infarct is soft (liquefactive). It may be pale or hemorrhagic (depending on the cause).
- The infarct heals by gliosis (replacing small infarcts or encapsulating large infarcts). The brain surface opposite the infarct becomes depressed and the meninges at this site become thickened.

Remark: Brain infarcts may be:

- a) Pale due to thrombotic or embolic arterial occlusion or due to severe shock.
- b) Hemorrhagic due to venous occlusion (jugular vein thrombosis).

Microscopy:

The infarct appears structureless with breaking of myelin. Microglia cells engulfing fat globules of the broken myelin, appear swollen with pale cytoplasm and are called compound granular corpuscles. Congestion, hemorrhage and neutrophils may be seen.

Clinical Effects: They vary according to site of infarction. Hemiplegia occurs if the internal capsule is affected. Some other cases may be fatal.

4) Heart (Myocardial) Infarction:

It is one of the major causes of death. The details are discussed in chapter 1 of systemic pathology.

5) Splenic Infarction:

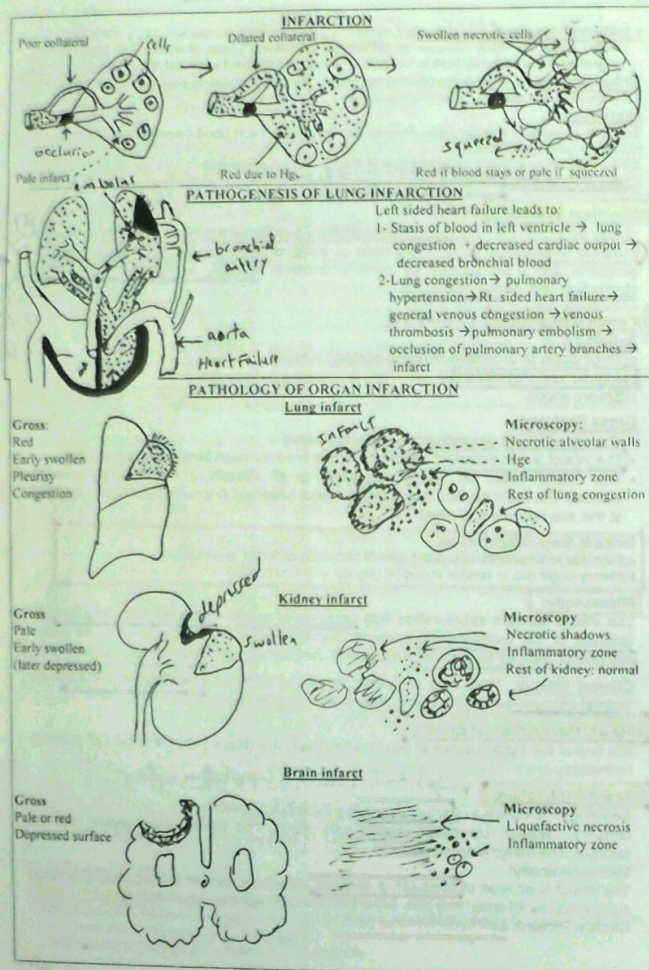
Aetiology: Occlusion of splenic artery by thrombus or embolus.

Grossly: Wedge (pyramidal)-shaped pale infarct. The serosal base shows fibrinous exudate. The margins are hyperemic.

Microscopically:

The infarct is an area of coagulative necrosis showing ghosts of splenic pulp structures surrounded by inflamed margins. Later the infarction appears structureless.

Clinical Picture: Left hypochondrial pain.



6) Kidney Infarction:

Aetiology: Thrombotic or embolic occlusion of the renal artery.

Grossly: Wedge shaped pale infarct. The kidney is retroperitoneal, so no fibrinous inflammation occurs. Margins are hyperemic.

Microscopy:

The infarct is an area of **coagulative necrosis** showing ghosts of renal glomeruli and tubules surrounded by inflamed margins. Later the infarct appears structureless.

Clinical Effect: Hematuria occurs. Pain is minimal.

Remark: Two major types of ischemic renal necrosis occur:

- 1- Localized renal infarction due to thrombosis or embolism.
- 2- Diffuse bilateral renal cortical necrosis (acute tubular necrosis, bilateral diffuse infarction) as in cases of severe shock.

7) Other examples of infarction:

Liver infarction is rare & is caused by occlusion of the main hepatic artery by thrombosis or surgical ligation. *↳ Liver receives + double blood supply*

Ovarian or testicular infarction: are uncommon & occur in cases of ovarian or testicular twisting.

(Infarction of extremities occurs most commonly in legs (see dry gangrene))

+ rapidly eating side = *dry* =

GANGRENE

DEFINITION: Gangrene is **massive necrosis** (caused by acute ischemia or severe bacterial infections) followed by putrefaction.

AETIOLOGY: *↳ necrosis + putrefaction*

1) Causes of Necrosis:

- **Acute Ischemia:** See before. *↳ has 81% x*
- **Bacterial infections:** See infective gangrene below.

2) Putrefaction: It is caused by action of certain bacteria (saprophytes), which normally exist in the human body but **cannot act except on dead tissues**. These bacteria decompose the dead tissue leading to liberation of hydrogen sulphide. **Reaction between hydrogen sulphide and iron (of blood hemoglobin within the area) leads to formation of iron sulphide, which gives the gangrenous tissue black coloration.**

TYPES OF GANGRENE:

1-Dry gangrene 2-Moist gangrene 3-Infective gangrene 4- Gas gangrene.

1- DRY GANGRENE

Pathogenesis:

Dry gangrene occurs in limbs and is considered as limb infarction rather than gangrene, since putrefaction in dry media is minimal and slow (therefore toxemia is slight). Dry gangrene of limbs is due to arterial occlusion, while veins are patent. Gangrene in such cases is dry because:

- Limbs are not rich in tissue fluids due to **surface evaporation**.
- Distal to arterial occlusion, **tissue fluid formation will stop**, but since veins are patent, the already present tissue fluid will be drained into the veins as normal.

Examples:

- Senile gangrene (commonest example) : see below
- Arterial embolism (uncommon).
- Buerger's Disease (thromboangiitis obliterans)
- Raynaud's disease (arterial spasm).
- Early phase of diabetic gangrene: see below

Activity

Define - Sp of Dry

SENILE GANGRENE

VIP

مؤهل لوجه

Predisposing factors:

- At old age there is gradual narrowing of arteries due to atherosclerosis.
- At old age, weak cardiac action leads to vascular stasis.
- Because of the above factors thrombosis is common and may occur spontaneously or after a slight injury induced by e.g. wearing tight shoes.

Pathological Features: Gangrene usually starts at the big toe & progresses as follows:

- Distal to occlusion** (e.g. the big toe) the following events occur:
 - The area appears pale and cold due to ischemia.
 - Then it appears red due to escape of blood from necrotic capillaries.
 - Then it gradually becomes black.
- Progression of the gangrenous process:**

Living tissue adjacent to the gangrenous area are irritated. The already atherosclerotic arteries may undergo further thrombosis leading to progression of the gangrenous process. The process may be repeated and in this way gangrene progresses proximally till it reaches an area with good arterial collateral circulation e.g. around the ankle. At this level gangrene stops.
- Line of demarcation:** This is a red zone of acute inflammation seen at the margin of the black gangrenous area. It is due to irritant products released from the dead gangrenous tissues.
- Line of separation:** This is a groove that appears in the vicinity of the line of demarcation. It gradually deepens until the dead gangrenous part separates from the viable (living) tissues. The resulting stump is conical in shape, because muscles and bones separate at a lower level than skin (this is because the arterial collaterals extend efficiently at a lower level in bones and muscles).

2- MOIST GANGRENE (WET GANGRENE)

Moist gangrene occurs in circumstances with rich tissue fluid such as in internal organs e.g. intestine, diabetic gangrene (due to infection → fluid exudate) & when both artery and vein are occluded (as limb tight tourniquet). Putrefaction in these cases is rapid & toxemia is marked. Line of demarcation is poor & self separation does not occur as in dry gangrene. The main differences between dry & moist gangrene are listed in this table:

DRY GANGRENE	MOIST GANGRENE
1) Due to arterial occlusion.	1) Due to occlusion of both artery and vein.
2) Occurs in limbs in cases of: - Senile gangrene. - Burger's disease. - Raynaud's disease. - Early diabetic gangrene.	2) Occurs in limbs in cases of: - Crush injuries. - Tight tourniquet. - Bed sores. - Diabetic gangrene.
3) Does not occur in internal organs.	3) Occurs in internal organs (intestine), it is more serious than moist gangrene of limbs, because internal organs are rich in tissue fluid (no surface evaporation) and because saprophytes exist in large numbers in the intestinal lumen.
4) Very slow putrefaction.	4) Rapid putrefaction in limbs, very rapid in case of intestinal gangrene.
5) Mild toxemia.	5) Severe toxemia.
6) Gangrenous part is dry and mummified.	6) Gangrenous part is oedematous & swollen.
7) Prominent line of demarcation.	7) Poor demarcation.
8) Line of separation.	8) No line of separation.

* Auto Amputation

* no Auto Amputation
hence no separation line

مرض السكر أو مرض كيتوس من قصب السكر

Define

DIABETIC GANGRENE

- Diabetes leads to atherosclerosis, which may be complicated by thrombosis.
- Trophic changes (due to sensory loss) make slight injuries pass unnoticed.
- Sugar in tissues and low immunity favor infection → fluid exudation & vascular thrombosis.

Pathology:

Diabetic gangrene may start dry (due to arterial thrombosis), but more commonly it is a combination of moist and infective gangrene. The exudative changes due to infection make the area oedematous and moist. The gangrenous process is accompanied by severe toxemia and limb amputation may be life saving. In most of cases it starts in the big toe and then progresses with no tendency towards demarcation or self-separation.

Moist

INTESTINAL GANGRENE

It is a very serious type of moist gangrene; the intestine is rich both in tissue fluids and saprophytes, and therefore gangrene extends very rapidly. The causes of intestinal gangrene include mesenteric vascular occlusion, intussusception, volvulus, strangulated hernia. There is intestinal obstruction, peritonitis and severe toxemia. It is more serious than diabetic gangrene.

Moist

3-INFECTIVE GANGRENE

It is considered a subtype of moist gangrene. It is called infective gangrene because necrosis is caused by bacteria followed by putrefaction by saprophytes. Examples of infective gangrene:

- Lung gangrene** due to putrefaction of lung abscess.
- Bed Sores** These are skin ulcers that develop over bony prominences (sacrum and greater trochanters) in cases of prolonged recumbence due to paralysis, bone fractures or coma. They are due to ischemic necrosis and secondary bacterial infection.
- Cancrum oris:** This is oral gangrene affecting debilitated children.
- Other types e.g. noma pudendi:** Infective gangrene of the vulva, usually in debilitated children. **Fournier gangrene** (idiopathic spontaneous fulminating gangrene of the penis and scrotum) & **necrotizing Fasciitis** (due to mixed aerobic and anaerobic infections, most commonly in diabetics and is rapidly fatal. It is restricted to the fascia and does not affect the underlying muscles).

Moist

4- GAS GANGRENE

Definition: A subtype of infective gangrene characterized by production of several gases (hydrogen, carbon dioxide, hydrogen sulphide...) It is commonly fatal due to severe toxemia.

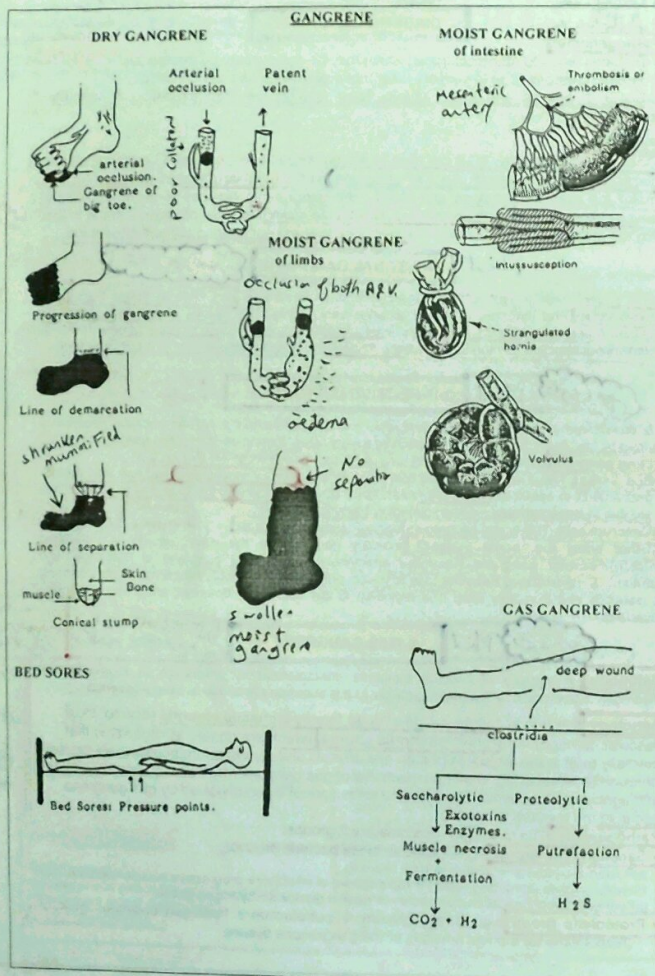
Aetiology: It is due to contamination of deep locally ischemic wounds (due to local vascular damage) with certain clostridia spores which are anaerobic organisms that normally exist in the intestines of man and animals and can therefore contaminate the soil (through fecal material). Common examples of gas gangrene are seen in battle casualties and agricultural accidents. Superficial wounds cannot be complicated by gas gangrene because the medium is aerobic.

Pathogenesis:

- The causative clostridia are 2 groups:
 - Saccharolytic group** e.g. *C. Cl. welchii*, these bacteria produce:
 - Powerful exotoxins → severe muscle necrosis.
 - Hyaluronidase (spreading factor) → rapid spread of infection → progressive muscle necrosis.
 - Fermentation of muscle carbohydrates → carbon dioxide & hydrogen gases.
 - Proteolytic group** e.g. *C. Cl. histolyticum* → putrefaction → hydrogen sulphide gas (responsible for the foul smelling of the gangrenous tissues)

* no Pus no urinary bladder gangrene bec saprophytes are aerobic
Phosphor can occur gangrene

White Knightlane



DEFINITION:

Oedema is accumulation of abnormal amounts of fluid in the intercellular tissue spaces and/or body cavities. Oedema fluid may be transudate (the normal tissue fluid but in amounts exceeding the normal), exudate (inflammatory fluid) or lymph.

A comparison between transudate and exudate is listed in the following table:

TRANSUDATE	EXUDATE
• Low protein content below 3g/dl	• High protein content above 3g/dl
• Protein content mainly albumin	• Protein content mainly fibrinogen
• Does not clot (no fibrinogen)	• Undergoes clotting
• Low specific gravity below 1015	• High specific gravity above 1015
• Poor cellularity.	• Rich in inflammatory cells

CAUSES & PATHOGENESIS OF OEDEMA

1) **Increased Capillary Hydrostatic Pressure** as in cases of venous congestion
2) **Sodium and water retention** due to renal disease as glomerulonephritis, heart failure (due to decreased glomerular perfusion) and in cases of hyperaldosteronism. Salt and water retention → increased capillary hydrostatic pressure.

3) **Decreased Colloid Osmotic Pressure Of Plasma** due to hypoproteinaemia (fall of total serum proteins below 2.5 gm%, or fall of serum albumin below 1.5 gm%).

Remark: The normal colloid osmotic pressure (O.P) is about 20 mm Hg. The O.P is an opposing force to the hydrostatic pressure. Normally at the arterial end filtration of tissue fluid (transudate) occurs because the hydrostatic pressure (35 mm Hg) is higher than the O.P (20 mm Hg). At the venous end the O.P (20 mm Hg) is higher than the hydrostatic pressure (15 mm Hg) resulting in withdrawal of the tissue fluid. Therefore fall of osmotic pressure (due to hypoproteinaemia) results in oedema, which will be generalized.

4) **Increased Capillary Permeability** as in inflammation & hypersensitivity. Escape of proteins in the oedema fluid will lower the plasma osmotic pressure & raises the tissue osmotic pressure → further oedema.

5) **Increased Tissue Osmotic Pressure**: It is usually secondary to increased capillary permeability (e.g. in inflammation). See above.

6) **Lymphatic Obstruction** as in cases of:

- **Filariasis** (the adult parasites live inside lymphatics). Oedema affects limbs & genitalia. The affected limb may be massively swollen (elephantiasis).
- **Lymphatic permeation by malignant cells as in breast cancer** → **breast oedema**.
- **Surgical removal of lymphatics** (as in cases of radical mastectomy which is surgical removal of breast & axillary lymphatics for treatment of breast cancer) → Lymphatic oedema (affects arms in case of radical mastectomy).
- **Post-irradiation** (for treatment of cancer): Irradiation may lead to severe fibrosis ending in lymphatic obstruction.
- **Lymphangitis and lymphadenitis**.
- **Congenital hypoplasia of lymphatics** (Mieroy's Disease).

Remark: in our normal tissues, part of the tissue fluid is withdrawn at the venous end of capillaries while the other part changes into lymph which is drained by lymphatics (through which it reaches the circulation). Therefore lymphatic obstruction results in oedema.

CLASSIFICATION: TYPES OF OEDEMA:

1) **Localized or Generalized:**

Localized Oedema:

a) **Inflammatory oedema** (due to acute inflammation). Oedema fluid is exudate.

b) Obstructive oedema: venous & lymphatic subtypes:

- **Venous obstruction:** Localized venous congestion → transudative oedema. Examples:
 - Oedema of leg due to venous thrombosis or late in pregnancy.
 - Lung oedema due to left sided heart failure
 - Ascites due to portal hypertension as in case of liver cirrhosis or bilharzial portal fibrosis.
- **Lymphatic oedema** due to lymphatic obstruction (see above). Oedema fluid is lymph.

Generalized Oedema (anasarca):

a) **Cardiac oedema** due to right sided heart failure (see before and describe).

b) **Nutritional oedema** due to hypoproteinaemia in cases of:

- Malnutrition (famine oedema).
- Malabsorption states.
- Chronic liver disease (decreased synthesis of plasma proteins)

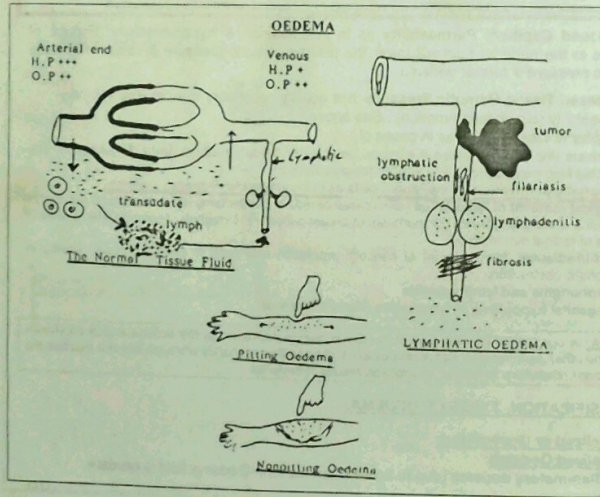
c) **Renal oedema:**

- Nephrotic type due to nephrotic syndrome e.g. due to renal amyloidosis.
- Nephritic type due to nephritic syndrome occurring in some cases of glomerulonephritis as acute post-streptococcal glomerulonephritis. It is due to immune-mediated increase of capillary permeability as well as salt & water retention (see systemic pathology). It particularly starts in the eye lids then becomes generalized.

2) Pitting or Non-pitting :-

Pitting Oedema: In all types of generalized oedema and in the congestive type of localized oedema, the fluid is transudate which is poor in proteins and does not clot on standing. This fluid can be easily displaced on pressing the affected part leaving a pit at site of pressure.

Non-pitting (hard) Oedema: It occurs in cases of lymphatic oedema & sometimes in inflammatory oedema.



6- HEMORRHAGE

VIP

Definition + effect of pathogenesis

DEFINITION: Escape of blood outside the cardiovascular system.

AETIOLOGY: Apart from physiological loss of blood (menses) causes of bleeding include:

Local causes of bleeding as:

- Traumatic injury of vessels: accidents, surgery. Trauma → accident
- Erosion of vessels e.g. in case of malignant tumors, tuberculosis & peptic ulcers.
- Rupture of aneurysm. Rupture of Blood vessel
- Local venous congestion.
- Inflammations e.g. bilharzial cystitis, dysentery, bronchitis.

General Causes of bleeding:

- Hypertension and general venous congestion.
- Blood diseases as hemophilia, purpura and leukemia.
- Vitamin C or K deficiency. Deficiency

Remark: Apart from traumatic bleeding; hemorrhage due to other causes occurs spontaneously.

TYPES OF HEMORRHAGE:

1) External Hemorrhage:

a) Form skin.

b) Form respiratory tract:

- Epistaxis: bleeding from the nose.
- Hemoptysis: coughing blood. The blood is red frothy (mixed with air & alkaline)

c) From alimentary tract:

- Hematemesis: vomiting of blood (due to bleeding in duodenum, stomach or oesophagus). The blood is brownish, acidic & contaminated by food particles.
- Melena: passage of dark digested blood in stools. This is due to bleeding from duodenum, stomach or oesophagus. Remember: causes of hematemesis & melena are the same. Small Intestinal Cancer = above ileocecal valve
- Bleeding per rectum: passage of red undigested blood with stools. It is due to bleeding from below the duodenum. In such cases vomiting does not occur.

d) Form urinary tract: hematuria

e) Form female genitalia:

- Menorrhagia: excessive or prolonged menses
- Metrorrhagia: Irregular uterine bleeding.

2) Internal Hemorrhage: This is bleeding into body cavities

- a) Hemothorax: hemorrhage in the pleural sac
- b) Hemopericardium: hemorrhage in the pericardial sac
- c) Hemoperitoneum: hemorrhage in the peritoneal sac
- d) Hematocele: hemorrhage inside tunica vaginalis sac
- e) Hemarthrosis: hemorrhage inside joint cavities.

3) Interstitial Hemorrhage: This is hemorrhage in the interstitial tissue spaces

- According to type of bleeding vessels: It may appear red (arterial) or blue (venous blood). Gradually this color changes green (due to bileverdin derived from hemoglobin) then brownish due to hemosiderin (also derived from hemoglobin). These pigments are gradually absorbed & removed by macrophages, so the color of the area gradually returns normal.

* Blood of menses non Coagulable bec. dead endometrium
 → proteolytic enzyme
 → no fibrinogen

White Knightlane

وما كان يعصوا الحقيقت ولا علم

benign tumours ≠ swelling

According to its extent, interstitial hemorrhagic may be:

- Petechial (small spots of hemorrhage) 3ml
- Ecchymosis (a bigger patch or patches of hemorrhage) 3cm
- Hematoma (large blood swelling)

EFFECTS OF HEMORRHAGE:

1) Local Effects: Hemostasis (Natural Arrest Of Hemorrhage):

- Mechanism of hemostasis:**
 - Hypotension (due to blood loss) → reduced rate of bleeding.
 - Curling of the endothelium → minimize bleeding.
 - Vascular constriction by serotonin released from platelets at site of vascular leakage.
 - Clotting of blood around site of injury (due to platelets) → clotting not thrombus
 - Gradual fibrous organization of the clot → permanent arrest of hemorrhage.

• Causes of failure of hemostasis:

- Large vascular injury
- Coagulation defects & blood diseases
- If infection occurs before clot organization, softening of the clot occurs (by proteolytic enzymes) → hemorrhage occurs again (secondary hemorrhage).

2) Systemic Effects:

a-Chronic (repeated) blood loss: as in cases of bilharziasis → iron deficiency anemia

b-Rapid blood loss: The effects depend on the amount of hemorrhage:

- Very small amount** → No effect.
- Moderate amounts** less than 750-1000 ml of blood: Compensation is the rule by:
 - Release of catecholamines (from the suprarenal glands), renin (from the kidney) & antidiuretic hormone (from posterior pituitary) will cause vasoconstriction & restoration of the blood pressure.
 - The initial fall in the hydrostatic pressure leads to withdrawal of tissue fluid into the blood thus increasing the blood volume and pressure.
 - Decreased renal flow causes salt and water retention.
 - Blood cells (from bone marrow) & plasma proteins (from liver) are restored gradually.
- Massive amounts** more than 1 liter lead to shock (see below).

7- SHOCK

VIP

DEFINITION: Shock is sudden widespread hypoperfusion of cells and tissues due to a variety of causes leading to decrease of the effective circulating volume of blood.

CLINICAL PICTURE:

- Hypotension
- Weak rapid pulse
- Shallow rapid respiration
- Oliguria or anuria
- Patient is restless & anxious or apathetic
- Skin is pale, cool & sweaty (however in cases of shock due to peripheral vasodilatation as septic shock the skin may be warm and flushed).

pale + shock → septic shock except one

Ischemia = Localized shock ≠ Shock

STAGES OF SHOCK:

If the cause of shock is a massive insult (e.g. massive hemorrhage due to ruptured aortic aneurysm and massive myocardial infarction), the condition is very rapidly lethal. Otherwise shock passes in three stages:

1) The early nonprogressive phase: There is release of catecholamines and antidiuretic hormone as well as activation of the renin-angiotensin axis, resulting in peripheral vasoconstriction (sparing the coronary and cerebral vessels). At this early phase, therapeutic maneuvers have the best chance of success.

2) Progressive phase: Uncorrected shock passes imperceptibly to the progressive phase during which the vital organs begin to experience severe hypoxia due to progressive reduction of tissue perfusion. This oxygen deficit is followed by anaerobic glycolysis leading to production of lactate and hence lactic acidosis. The consequent reduction in pH of the tissues result in vasodilatation of arterioles leading to progressive pooling of blood in the microcirculation.

3) Irreversible phase: At some point, the decreased tissue perfusion results in irreversible injury leading to failure of multiple organ systems (renal, cardiac, cerebral, respiratory, etc).

TYPES, CAUSES & PATHOGENESIS OF SHOCK:

1) Hypovolemic Shock: Cause of hemorrhage + shock

Pathogenesis: It is due to sudden reduction of blood volume & hence fall of blood pressure & reduction of cardiac output. See stages of shock & describe

Causes:

- Severe hemorrhage (post hemorrhagic shock), due to trauma, surgery, blood diseases... etc.
- Severe fluid loss (dehydration) in cases of:
 - severe diarrhea or vomiting
 - severe burns due to loss of fluid from damaged blood vessels

2) Cardiogenic shock:

Pathogenesis: It is due to failure of myocardial pump and hence low cardiac output & fall of blood pressure (see stages of shock & describe).

Causes:

- Myocardial infarction due to coronary occlusion
- Rupture of a valve
- Rupture of heart
- Severe arrhythmias
- Cardiac tamponade
- Massive pulmonary embolism

3) Shock Due to Peripheral Sequestration of the Blood Volume: = V.D in all capillaries

It is due to peripheral pooling of blood within the capillary bed due to peripheral vasodilatation leading to reduction of blood volume and hence low cardiac output (see stages of shock & describe). Shock due to peripheral sequestration of the blood volume may be due to:

a-Septic shock (Endotoxic shock)

Causes: It is due to severe gram negative bacterial infections (and less commonly gram positive bacteria), as in cases of septicemia caused by E. coli, streptococci, meningococci. It is more common in cases of immunodeficiency states as in immunosuppressed persons and in cancer patients under chemotherapy.

Pathogenesis: Endotoxins lead to the following effects:

↑ G-ve factor, ↓ blood = endotoxic shock → shock + death

↑ TNF + ↑ prostaglandins → ↑ endothelium → ↑ permeability → ↑ fluid loss + ↑ capillary leak → ↓ blood volume

↑ Antinflammatory + Polymers

peripheral sequestration of blood volume

* Septic shock $\rightarrow$ pathology $\rightarrow$ endotoxin of Gram

- They activate complement & lead to degranulation of mast cells $\rightarrow$ histamine $\rightarrow$ peripheral vasodilatation & peripheral blood pooling.
- They stimulate the monocytes to release TNF & other chemical mediators $\rightarrow$ increased vascular permeability $\rightarrow$ reduction of the effective circulating blood volume.
- They activate the clotting system $\rightarrow$ DIC (disseminated intravascular coagulation).

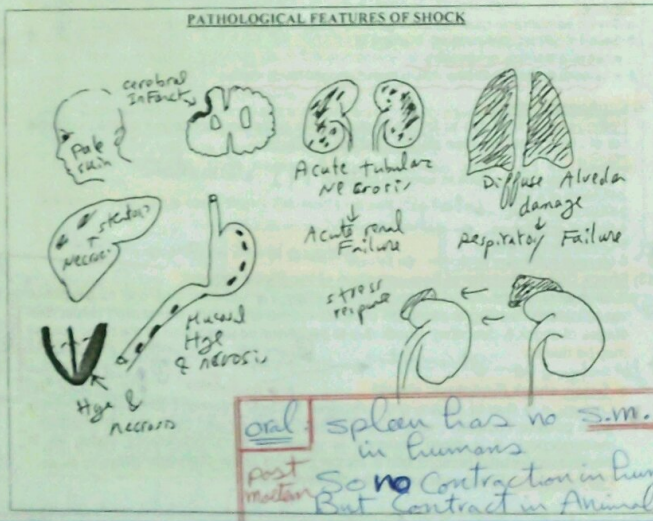
b-Neurogenic shock due to spinal cord injury or anesthesia resulting in neurogenic mediated vasodilatation & fall of blood pressure

c-Anaphylactic shock: See later for type I hypersensitivity *generalized*

PATHOLOGICAL FEATURES OF SHOCK: (Post-mortem picture of shock):

- Skin is pale, but may be flushed as in cases of septic shock.
- Brain shows ischemic changes: cerebral infarcts may develop.
- Kidneys: Acute tubular necrosis (bilateral renal cortical necrosis).
- Lungs: Diffuse alveolar damage (this clinically results in adult respiratory distress syndrome) **(DAD)** *due to ischemia problems*
- The adrenals show features of the "stress response", mainly loss of the adrenal lipids.
- Liver: Steatosis and necrosis.
- GIT: Patchy mucosal hemorrhage and necrosis. *necrosis*
- Heart:
 - a) Subendocardial and subpericardial hemorrhages and necrosis.
 - b) Hypercontraction of myocytes.

PATHOLOGICAL FEATURES OF SHOCK



* Neonatal Respiratory distress syndrome = NRDS
= due to $\downarrow$ Surfactant

DISORDERS OF IMMUNE REACTION

ANTIGENS & ANTIBODIES

- **Antigen** is a foreign protein substance that can evoke an immune response mediated by B lymphocytes (plasma cells) or T lymphocytes. A **hapten** (incomplete antigen) is a nonprotein foreign substance (e.g. drug) that can evoke an immune response by combining with one of the body proteins (where this combination acts as an antigen). When a tissue structure is considered antigenic is called **autoantigen** and leads to an autoimmune disease.
- The antibodies are proteins secreted by plasma cells (which are derived from B lymphocytes after antigen stimulation), called **immunoglobulins** including IgA, IgG, IgM, IgE & IgD, while secretions of T lymphocytes are called **lymphokines**. It is to be remembered that B lymphocytes are derived from bone marrow, while T lymphocytes are derived from the thymus.
- Antigen-antibody reactions represent two faces of one coin. They may be useful if the antigen is a living irritant (infection) as tuberculosis, but if the irritant is nonliving the reaction will be pure hypersensitivity. Thus types of antigen-antibody reactions include:
 - 1-Immunity: A useful reaction against living irritants resulting in their elimination. It is a useful
 - 2-Hypersensitivity: A harmful reaction against living irritants (bacteria, virus, spore or non living irritants (such as food proteins, dust, pollens, drugs, etc) leading to tissue destruction.

IMMUNITY

This is body defense mechanisms aiming at disposal of living irritants. *living irritants divided into*

- **Nonspecific immunity** including phagocytosis (macrophages and neutrophils) and other cells (nonspecific cytotoxic cells), opsonins (antibodies that help phagocytosis) and lysozyme in saliva and other body secretions.
- **Specific (acquired) immunity** which is of two types:
 - 1-**Humoral immunity**: Serum antibodies (immunoglobulins IgG, IgM, IgA, IgD & IgE) are secreted by plasma cells. Plasma cells develop from stimulated B lymphocytes. Examples of useful antibodies include bacteriolysins, agglutinins & others.
 - 2-**Cell-mediated immunity**: Lymphokines (cellular antibodies) are secreted by stimulated T lymphocytes. These lymphokines have several functions e.g. stimulation of macrophages to engulf an organism.

IMMUNOPATHOLOGY:

- This is the study of abnormalities of the immune response which may be:
- Exaggerated response called **hypersensitivity** or **allergy**. There are 4 main types: I, II, III & IV. I, II, III are mediated by immunoglobulins and develop rapidly (**immediate hypersensitivity**) while type IV is mediated by sensitized T-cells (cell-mediated) and the reaction develops over a longer time, up to several days (delayed hypersensitivity). Hypersensitivity may develop along two main steps; starting with introduction of the antigen for the first time which stimulates antibody formation; but by that time the antigen may have been eliminated from the system. The second step is re-introduction of the same antigen which reacts with the already formed antibodies.
 - Loss of tolerance, where some of the normal tissue components are considered antigenic (autoantigens) $\rightarrow$ autoantibodies $\rightarrow$ tissue destruction & development of disease. This is called **autoimmunity** & is also classified among hypersensitivity states.
 - Deficient response (**immunodeficiency**) involving B or T lymphocytes, macrophages, complement and may be congenital, inherited or acquired. Examples:
 - 1-X-linked agammaglobulinemia of Bruton, congenital thymic hypoplasia (DiGeorge syndrome), isolated IgA deficiency (which may be hereditary familial or acquired following infection with toxoplasmosis, measles or other viral infections).
 - 2-Acquired as AIDS, drug-induced immunodeficiency (e.g. interferon & diabetes mellitus).

TYPE I HYPERSENSITIVITY (Immediate Hypersensitivity)

Mechanism:

Introduction of the antigen for the first time stimulates IgE formation, which becomes fixed to the surface of mast cells. Re-exposure to the same antigen produces reaction with IgE fixed on the mast cell surface resulting in liberation of histamine and other chemical mediators leading to:

- Tissue necrosis.
- Vasodilatation (which in systemic reactions leads to hypotension)
- Allergic inflammation characterized by excess fluid exudate (oedema) and eosinophils
- Bronchospasm
- Increased mucus secretion by mucous glands

Examples:

1-Anaphylactic Shock:

- May follow rupture of hydatid cyst, injection of penicillin or antitoxic sera....
- Manifestations develop within minutes and include:
 - Urticaria
 - Bronchospasm
 - Generalized oedema
 - Hypotension, shock and sometimes death.

2-Atopy (Atopic Diseases):

- Atopy means strange. This type of hypersensitivity has genetic predisposition.
- Examples of Atopic Diseases include bronchial asthma, allergic rhinitis & allergic conjunctivitis.
- Atopy differs from anaphylaxis in that IgE production is localized within a certain tissue or organ in contrast to the systemic production of IgE in case of anaphylaxis.
- Prausnitz-Kustner reaction: If serum (containing antibodies) from patient with an atopic disease is injected in the skin of a normal person, followed by injection of the specific antigen at the same site, a skin hypersensitivity reaction may occur.

TYPE II HYPERSENSITIVITY (Cytotoxic Hypersensitivity)

Mechanism:

- The antigen is a component of a cell membrane.
- The antibodies are of the IgG and IgM classes.
- The reaction requires complement activation.
- The target cells undergo lysis.

Examples:

- Incompatible blood transfusion.
- Rh incompatibility (erythroblastosis foetalis).
- Some types of rejection of transplanted organs.
- Autoimmune hemolytic anaemias.

TYPE III HYPERSENSITIVITY (Immune Complex Reaction)

Mechanism:

- The antibodies (IgG and IgM) combine with the antigen producing immune complex
- The immune complexes are trapped within the vascular basement membranes.
- Complement activation leads to lysis and destruction of the basement membrane.

Examples:

- Acute proliferative post-streptococcal glomerulonephritis.

- Arthus reaction: Repeated subcutaneous injection of antigens (e.g. insulin) producing local vasculitis, necrosis, oedema and hemorrhage due to type III hypersensitivity.
- Serum sickness:
 - The antigen is serum- injected for the first time in large amounts.
 - Part of the antigen will, still be present by the time the antibodies are formed (about 10 days after injection of the antigen).
 - Immune complexes are formed producing systemic manifestations including: Urticaria, fever, joint pains, generalized lymph node enlargement and glomerulonephritis.
- Some autoimmune diseases as SLE.

TYPE IV HYPERSENSITIVITY (Delayed Hypersensitivity)

Mechanism:

- The antigen is a part of a microorganism: bacteria as tuberculosis, virus, fungus or parasite
- The antigen stimulates T lymphocytes → Sensitized T lymphocytes → lymphokines of several types, of which some → cell mediated immunity (e.g. by attracting macrophages & inhibiting their migration from the area) & other lymphokines cause type IV hypersensitivity by causing necrosis

Examples:

- Caseous necrosis in tuberculosis and tuberculin skin test.
- Cell-mediated graft rejection.
- Contact dermatitis.
- Some autoimmune diseases.

AUTOIMMUNE DISEASES

DEFINITION: These are hypersensitivity diseases resulting from destruction of one or more of the body tissues or organs by autoantibodies.

MECHANISM:

Autoimmune diseases are due to a defect in the immune mechanism of self recognition; thus one of the body proteins is erroneously considered as "non-self" i.e it is considered antigenic, thus antibodies (autoantibodies) are formed leading to tissue destruction. The possible mechanisms include:

- **Altered tissue antigenicity** may be drug-induced, or produced by actions of microorganisms.
- **Cross reactions:** This may occur between some human structures and certain microbes (see pathogenesis of rheumatic fever).
- **Mutations of immunocompetent cells.**
- **Release of isolated proteins** e.g. thyroglobulin.
- **Imbalance of suppressor-helper T cell function.**
- **Genetic factors** play a role in some autoimmune diseases.

EXAMPLES of autoimmune diseases:

- Endocrine Diseases as Hashimoto's thyroiditis, 1ry myxoedema & 1ry Addison's disease.
- Some types of male infertility.
- Autoimmune hemolytic anemia.
- Gastrointestinal diseases as ulcerative colitis & Crohn's disease
- Liver diseases as autoimmune hepatitis, 1ry biliary cirrhosis & primary sclerosing cholangitis.
- Ocular diseases as sympathetic ophthalmia
- Disseminated sclerosis
- Collagen diseases.

★ COLLAGEN DISEASES (Connective Tissue Diseases)

Definition: A group of autoimmune diseases characterized by injury of collagen within & around vessels.

Pathology:

- The fragmented collagen fibers resemble a mass of fibrin. Therefore this is termed **fibrinoid necrosis** or fibrinoid degeneration. It is accompanied by inflammation.
- This is associated with increase of mucopolysaccharides within the ground substance.
- Finally **Fibrosis** develops which is the hallmark of disease state.

* Collagen diseases include:

- Rheumatic fever: See systemic pathology
- Rheumatoid arthritis: See systemic pathology
- Polyarteritis nodosa: See systemic pathology
- Systemic lupus erythematosus (SLE): See systemic pathology
- Scleroderma: characterized by systemic fibrosis affecting skin, GIT, lung, myocardium & kidneys
- Dermatomyositis: characterized by systemic muscle weakness (proximal > distal), eventually progressing to motor disability. In 50% of cases the disease is associated with skin rash.

* GRAFT REJECTION:

Tissue or organ transplantation (graft) from one person (donor) to another (recipient), as kidney, liver & heart should follow great precautions including:

- Donor selection: The histocompatibility (HLA) antigens of the donor and recipient should be matching. The results are excellent if the donor is the identical twin of the recipient.
- An immunological reaction in the donor against the graft is expected. Therefore post operative immunosuppressive therapy is important. However, still graft rejection can occur due to:
 - Hyperacute rejection:** Occurs when the recipient has been previously sensitized to antigens similar to those in the graft (e.g. blood transfusion) → immediate graft rejection within minutes up to 2 days. The mechanism is humoral (immunoglobulins and complement)
 - Acute rejection:** Occurs within a few days of transplantation or after cessation of immunosuppressive therapy. The mechanism includes cell mediated response (CD4+ / T helper & CD8+ cytotoxic cells) and is called acute cellular rejection → endothelial and parenchymal cell damage. It also includes acute humoral rejection due to antidonor antibodies → vasculitis
 - Chronic rejection:** Occurs within months to many years. It is characterized by vascular thickening → progressive graft ischemia → progressive graft destruction

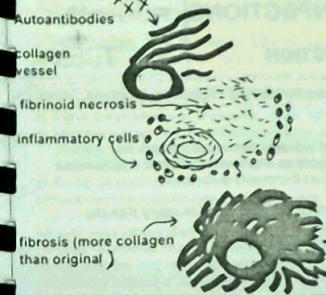
* GRAFT VERSUS HOST DISEASE (GVHD):

Bone marrow transplantation (e.g. in patients suffering from leukemia or aplastic anemia) may be followed by serious problems, one of which is GVHD, where the donor immunocompetent cells (lymphocytes) can evoke an immunological reaction against the recipient cells of a non HLA matching host. The reaction is mediated by CD8+ & CD4+ cells → host tissue destruction, particularly skin, biliary epithelium & GIT mucosa

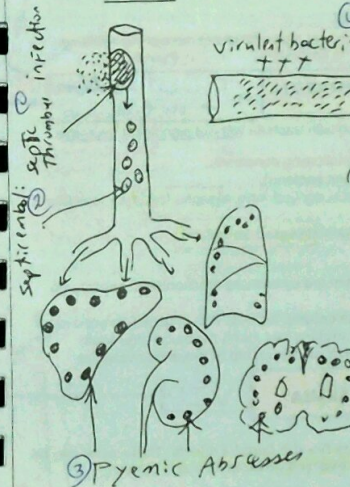
* IMMUNE RESPONSE AGAINST CANCER:

- The tumor cells have antigens (tumor associated antigens, TAA), capable of evoking an immune response.
- The immune response includes cellular factors as cytotoxic T cells, killer (K) cells, natural killer (NK) cells & activated macrophages. Humoral factors (immunoglobulins & complement) participate by an opsonin effect.
- Immunodeficiency states as AIDS & immunosuppressive therapy increase the incidence of development of some tumors in these patients as lymphomas and Kaposi sarcoma.
- Significance of immune response 1) Tumor regression in rare cases 2) Wide lymphocyte response against some tumors may carry favorable prognosis (e.g. medullary carcinoma of the breast)

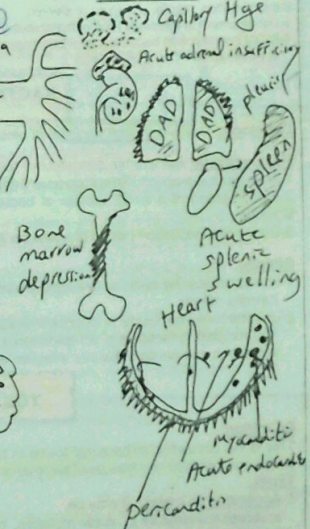
PATHOLOGICAL BASIS OF AUTOIMMUNE COLLAGEN DISEASES



PYAEMIA



SEPTICAEMIA



CHAPTER X

BACTERIAL INFECTIONS

INTRODUCTION

Definition: Infection is invasion of a living tissue by harmful organisms (bacteria, virus, fungus, parasites.)

Routes of infection:

- Exogenous by inhalation, ingestion or local contact with skin or mucous membranes.
- Endogenous from bacteria normally present in the body as intestinal E. coli, oral streptococcus viridans and respiratory pneumococci. Infection occurs if immunity is lowered.

Pathogenesis: The mechanisms by which bacteria can cause tissue injury include:

- Adhesion of bacteria to cells causing their death.
- Production of toxins which may be a) endotoxins b) exotoxins.
- Hypersensitivity reactions (mainly type IV).

Effects of bacterial infection:

- Cell injury: Necrosis and degeneration.
- Inflammation: acute, subacute or chronic.
- Development of immunity and/or hypersensitivity.
- Blood invasion with bacteria and/or bacterial products leading to one or more of the following:
 - Bacteremia
 - Toxemia
 - Septicemia
 - Pyemia

BACTERAEMIA

= Transient invasion + No toxemia

Definition: This is transient invasion of blood with bacteria without significant toxemia.

Pathogenesis: Bacteremia can occur in the following conditions:

- After tooth extraction (Streptococcus viridans bacteria).
- Blood spread of a small number of bacteria derived from a septic focus as tonsillitis & sinusitis.
- During the incubation period of some bacterial diseases as typhoid.

Effects:

- In most cases the bacteria are rapidly eliminated by immune mechanisms, causing no harmful effects.
- Uncommonly, the bacteria localize in tissue causing lesions. This is usually preceded by a predisposing factor, e.g. Streptococcus viridans that reach the blood after tooth extraction can cause subacute infective endocarditis on top of rheumatic valvulitis.

TOXAEMIA

VIP

Definition:

This is the circulation of bacterial toxins in the blood → harmful effects. These toxins may be endotoxins (released only from dead bacteria) or exotoxins (released from alive bacteria)

Types:

1. According to onset: It may be

- Acute toxemia** as in acute abscess, pneumonia, typhoid & diphtheria, cholera as well as in association with septicemia and pyemia.
- Chronic toxemia** as in chronic lung abscess & tuberculosis

2. According to type of bacterial toxins:

- Endotoxic toxemia:** as E coli, meningococcal & typhoid infections
- Exotoxic toxemia:** as cholera and diphtheria

3. Sepsaemia: It is a special type of toxemia occurring in cases of gangrene due to action of saprophytes on dead tissues → fatal

Pathological & Clinical Manifestations of Toxemia:

- Signs & symptoms of toxemia:** Fever, weakness, pallor, headache, rigors.
- Degenerations:** Mostly affect parenchymal cells as liver, kidney & heart in the form of cloudy swelling, hydropic degeneration or fatty degeneration. **Tissue necrosis** may also develop. Severe cases of toxemia (as in diphtheria) may lead to toxic myocarditis → acute heart failure.
- Acute adrenal insufficiency** due to hemorrhagic necrosis of adrenal cortex.
- Bone marrow depression** causing anemia. Leukopenia (instead of leukocytosis) may occur in severe cases.
- Acute respiratory distress syndrome** due to diffuse alveolar damage (DAD).
- Septic endotoxic shock** & disseminated intravascular coagulation (DIC). See before.
- Amyloidosis** may occur in cases of chronic toxemia (e.g. tuberculosis & chronic lung abscess).
- Selective effects of exotoxins:** e.g.
 - Enterotoxin of cholera → voluminous watery diarrhea and dehydration
 - Diphtheria toxins → neural paralysis & myocardial damage
 - Clostridium tetani toxins → severe muscle contractions (tetanic spasm)

SEPTICAEMIA

Definition:

A very serious commonly fatal condition in which large numbers of virulent bacteria circulate and multiply in blood accompanied by severe toxemia.

Aetiology:

- Causative bacteria:**
 - Cocci as Streptococcus hemolyticus (most common cause of septicemia), staphylococci & gonococci.
 - Bacilli as Bacillus anthrax & Bacillus proteus.
- Predisposing factor:** Low immunity as diabetics, terminal cancer & immunosuppressive therapy.
- Source of infection:** Septicaemia may complicate many conditions as:
 - Severe infections as meningococcus meningitis.
 - Ordinary infections as abscesses, cellulitis, puerperal sepsis, acute osteomyelitis, post-operative infections, infected wounds and even infection following pin prick in low resistant patients.

Pathological Features of Streptococcus hemolyticus septicemia (other types of septicemia differ in few aspects). The effects are due to toxemia & bacterial invasion of tissues:

1. Effects of Acute Toxemia:

- Constitutional signs & symptoms of toxemia:** Fever, weakness, pallor, headache & rigors.
- Degenerations & necrosis**, particularly of parenchymal cells.
- Acute adrenal insufficiency** due to hemorrhagic necrosis of adrenal cortex.
- Bone marrow depression** causing anemia. Leukopenia (instead of leukocytosis) may occur in severe cases.

Acute respiratory distress syndrome due to diffuse alveolar damage (DAD).

2. Vascular & Hematological Disorders:

- Blood:** Hemolysis of RBCs. This leads to red staining of the intima of blood vessels.
- Capillary hemorrhages** (due to capillary destruction by bacterial toxins & enzymes). This leads to petechial hemorrhages in different parts of the body as in skin & mucous membranes.

→ vessels → Red due to red staining of intima due to hemolysis of RBCs

3-Serous Membranes: Serofibrinous or suppurative inflammation of pleura, peritoneum, pericardium....

4-Heart: a)toxic myocarditis b)acute infective endocarditis c) pericarditis.

5-Liver & Kidney: Toxic injury (cloudy swelling, fatty change, necrosis...).

6-Spleen: Acute splenic swelling. *enlarged + very soft consistency*
Gross: Enlarged, soft friable spleen with doughy cut surface showing hemolysed blood.
Microscopy: the sinusoids are filled with neutrophils and macrophages (including Littoral cells). Lymphoid follicles are early hyperplastic but may under go necrosis and atrophy.

PYAEMIA

Definition:

It is the development of multiple small abscesses (pyaemic abscesses) within one or more organs caused by the circulation of septic emboli derived from septic thrombi. Commonly fatal

Mechanism (pathogenesis):

- The condition starts by development of septic thrombi, most commonly in veins in cases of septic thrombophlebitis and less commonly in heart from septic valve thrombi (septic vegetations) in case of acute infective endocarditis. The causative bacteria are usually *Staphylococcus aureus*.
- Proteolytic enzymes derived from inflammatory cells will cause fragmentation of the septic thrombus → septic emboli.
- Septic emboli (multiple) will circulate in the blood, until they get impacted in the small blood vessels of organs. These small vessels are peripherally located in organs (while larger vessels are central or hilar).
- Multiple small abscesses (pyaemic abscesses) will develop in the vicinity of impacted emboli i.e adjacent to small vessels in the peripheral parts of organs.

Types:

- Pulmonary pyaemia:** It is due to septic thrombophlebitis of one of the systemic veins as a complication of abscess, cellulitis, osteomyelitis or other infections.
- Systemic pyaemia:** It may be due to the same causes of pulmonary pyaemia if some septic emboli are too small and could by-pass the lungs to reach the left side of the heart. Systemic pyaemia may be also due to septic thrombophlebitis of pulmonary veins in case of pulmonary infections. Septic vegetations of mitral or aortic valves in cases of acute infective endocarditis can similarly lead to systemic pyaemia.
- Portal pyaemia:** It is due to septic thrombophlebitis of one of the venous tributaries of the portal vein e.g. in cases of acute cholecystitis or acute appendicitis. Septic emboli in the portal circulation cause pyaemic liver abscesses.

Pathological Features:

1-Distribution: Pyaemic abscesses develop in the lungs (in case of pulmonary pyemia), liver (in case of portal pyemia), or may be systemic affecting lungs, liver, kidneys, brain, spleen ... etc (in case of systemic pyemia).

2-Grossly

- Pyaemic abscesses are multiple, small & mostly superficially located within the affected organ. Their walls are hyperaemic and their centers show some pus.
- The surrounding tissues may show degeneration, particularly in parenchymal organs.
- Microscopically:** Debris, neutrophils, pus cells, macrophages, congested capillaries ... etc.
- Manifestations of toxemia** such as:

- Constitutional signs & symptoms of toxemia: Fever, weakness, pallor, headache, rigors.
- Degenerations & necrosis, particularly of parenchymal cells
- Acute adrenal insufficiency due to hemorrhagic necrosis of adrenal cortex.
- Bone marrow depression → anemia *Leucocytosis may occur but leukopenia is more common.*
- Acute respiratory distress syndrome
- Septic endotoxic shock

→ difference point between Pyaemic abscesses & T.B. Micro

Puss by Staph → Dec produce Coagulase
not strept → septicemia

CHRONIC BACTERIAL INFECTIONS

Chronic bacterial infections may be :

- 1-Non-specific as chronic lung abscess.
- 2-Specific/ Granulomatous as a) Tuberculosis b) Leprosy c) Syphilis d) Actinomycosis

TUBERCULOSIS

DEFINITION: Tuberculosis is a chronic infectious granulomatous disease caused by *Mycobacterium tuberculosis* (tubercle bacilli)

AETIOLOGY:

- Predisposing factors:** Tuberculosis is common in communities with low standards of nutrition and housing (leading to low natural resistance of the people). The disease is common in Egypt.

The causative bacteria:

- The disease is caused by *Mycobacterium tuberculosis* (tubercle bacilli)
- There are several types of these tubercle bacilli, but only two types can cause disease in man: 1) *Human tubercle bacilli* and 2) *Bovine tubercle bacilli*.
- Tubercle bacilli are Gram-positive, acid-fast bacilli, best stained with Ziehl-Neelsen stain.
- The structure: the bacteria consists of an outer lipid capsule covering a body composed of a polysaccharide fraction and a protein component (tuberculinoprotein).
- Bacterial effect on tissues (pathogenesis): The bacteria do not produce toxins, but their tuberculinoprotein is strongly antigenic and the destructive lesions of tuberculosis are mainly attributed to hypersensitivity reactions. However, toxemia is common in tuberculosis due to secondary bacterial infection

Mode of infection: Tubercle bacilli reach the body either by inhalation or swallowing. Rarely the organisms are inoculated through skin abrasions.

1-Human Tubercle Bacilli: These bacteria are expectorated in sputum of patients having pulmonary tuberculosis. Bacteria can contaminate dust & survive for long periods in dust since they are resistant to drying. They infect other persons by:

- a) Inhalation of contaminated dust leads to lung tuberculosis.
- b) Swallowing of contaminated dust leads to tuberculosis of tonsils or intestine.
- c) Inoculation through skin is extremely rare.

2-Bovine Tubercle Bacilli: These bacteria exist in milk of tuberculous cows and are transmitted to man by swallowing of infected milk causing tuberculosis of tonsils or intestine.

TISSUE REACTION IN TUBERCULOSIS:

Infected tissues show one of two main types of reaction which may coexist:

i) THE PROLIFERATIVE TISSUE REACTION (THE TUBERCLE)

It is the basic lesion of tuberculosis. It develops around the tubercle bacilli. Several tubercles are formed and as they enlarge, they fuse together.

Mode of Formation of Tubercles:

- 1-Neutrophils are attracted within few hours to the polysaccharide fraction of the bacilli. They may engulf the bacilli but cannot digest them since the bacilli are protected by their lipid capsules, while neutrophils lack the enzyme lipase. Neutrophils die rapidly.

→ Mode of Transmission of Tubercle

2-Macrophages are attracted to the lipid part of the bacilli & accumulate gradually.

They engulf the bacteria & since macrophages contain lipase enzyme, they digest the lipid capsule of these bacteria → liberation of tuberculo protein in the cytoplasm of macrophages → alteration of macrophages which become swollen and pink resembling epithelial cells and are therefore termed **epithelioid cells**.

3-Some epithelioid cells fuse together forming giant cells called **Langhan's giant cells**.

4-T lymphocytes interact with macrophages that carry the bacterial antigenic material (tuberculo protein). This leads to sensitization of T lymphocytes. Sensitized T lymphocytes accumulated around the epithelioid cells in 10-14 days and release lymphokines which are responsible for development of **acquired immunity & hypersensitivity**. These lymphokines include the following important examples:

- Macrophage chemotactic factor (MCF)**: It attracts macrophages.
- Migration inhibition factor (MIF)**: It arrests the mobility of macrophages keeping them in the area.
- Macrophage activating factor (MAF)**: It promotes the bactericidal activity of macrophages.
- Ischemic factor**: Stimulates lymphocyte proliferation.
- Transfer factor**: Leads to sensitization of proliferation lymphocytes.
- Interferon**: It also activates macrophages to kill the organisms.
- Cytotoxic lymphokines**: These cause tissue necrosis (**caseation**).
- Skin reactive factor**: Leads to positive skin sensitivity test (tuberculin reaction).

★ Gross Features:

Tubercles are of microscopic size, but when they fuse they give rise to grossly visible small yellowish gray nodules; that may appear soft and cheesy due to caseation.

Microscopic Features: Each tubercle consists of:

- 1-Caseation necrosis** appears in the centre of the tubercle as pink structureless material. It is surrounded by epithelioid cells, giant cells and lymphocytes.
- 2-Epithelioid cells**: Large altered macrophages with abundant pink cytoplasm (resembling epithelial cells) indistinct cell borders and large vesicular nuclei. *not hyper*
- 3-Langhan's giant cells**: These are large cells with pink cytoplasm and several peripherally located nuclei forming a circle or U-shaped arch (horse shoe pattern). They engulf bacteria & caseous material.
- 4-Lymphocytes (mainly T cells)** form a peripheral zone.

Mechanism of caseation:

- 1-Hypersensitivity** (cytotoxic lymphokines). *T lymphocytes*
- 2-Ischemic necrosis** due to:
 - a) Tubercle formation is not accompanied by angiogenesis.
 - b) Endarteritis.

★ Fate of Tubercles:

- 1-Localization**: With adequate immunity the lesions heal by fibrosis (± dystrophic calcification):
 - a) Small lesions are totally replaced by fibrosis.
 - b) Larger caseous may be only surrounded by fibrosis (encapsulation). Some bacilli may however remain alive and dormant within the healed lesions, particularly the encapsulated ones. If later on the body resistance is lowered, these dormant bacilli lead to reactivation of tuberculosis.
- 2-Spread** of tuberculosis due to failure of localization.

Remember: Not all persons exposed to tubercle bacilli develop disease. After exposure, the fate may be good (localization) and many persons do not give symptoms, but it may be immediately bad (due to inadequate immunity & spread) or may later become bad (due to reactivation).

slowly
Proliferative
Comparison

II) THE EXUDATIVE TISSUE REACTION:

2 Conditions

- It has been found that tuberculous reaction in solid organs as liver & kidney is almost always proliferative, in serous membranes it is commonly exudative, while in lungs it is proliferative, exudative or combined.
- The typical exudative tissue reaction occurs in sensitized persons (having sensitized T lymphocytes).
- The exudative reaction is characterized by:
 - 1-Outpouring of fluid exudate containing fibrinogen.
 - 2-Numerous lymphocytes (and often neutrophils), but few epithelioid cells & giant cells.
 - 3-Caseation is usually marked & undergoes rapid liquefaction by enzymes derived from neutrophils.

SPREAD OF TUBERCULOSIS:

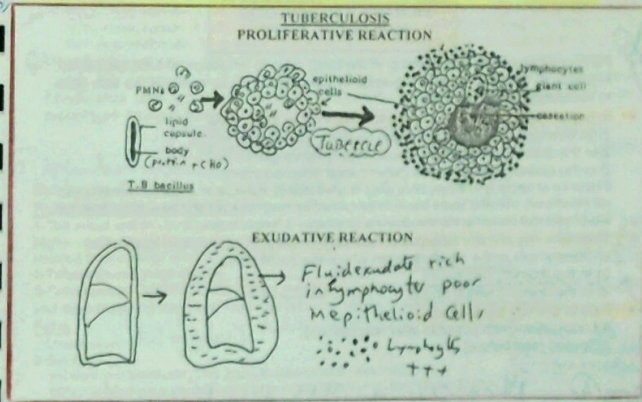
VIP

spread → 25

Mechanism of Spread: Tubercle bacilli are non-motile. Macrophages may carry the bacilli to different sites. Free bacilli can also be carried by tissue fluids, lymph or blood (following caseous destruction of vessels).

Routes of Spread: The main routes of spread are:

- 1-Direct spread** to the surroundings.
- 2-Lymphatic spread** to the draining lymph nodes.
- 3-Blood spread:** Effects largely depend on number of bacteria:
 - a) **No effects** may be produced if a small number of organisms reach the blood. These bacteria may be destroyed by the phagocytic cells of the different organs.
 - b) **Isolated organ tuberculosis:** The organisms settle in one or few organs causing lesions.
 - c) **Miliary tuberculosis:** A large number of bacteria reach the blood. The lungs, liver, kidneys, adrenals, serous membranes and other organs will show huge numbers of small adjacent tuberculous lesions: 1-2 mm each. The condition is rapidly fatal.
- 4-Intracanalicular spread:** e.g. coughed sputum may convey the bacteria to larynx, tonsils, tongue, etc.



Gross + Microscope + Fate = *answer*

FACTORS INFLUENCING THE COURSE OF TUBERCULOSIS:

- 1-Dose Of Infection and Virulence of the organism.
- 2-Immunity & Hypersensitivity:
 - a) Natural Innate immunity and general health of the individual is of great importance.
 - b) Degree of acquired immunity and delayed hypersensitivity. Both are mediated by sensitized T lymphocytes (cell mediated immunity). Hypersensitivity develops in 10-14 days after the onset of primary infection (delayed hypersensitivity type IV).

TYPES OF TUBERCULOSIS:

Primary Tuberculosis <i>Childhood type</i>	Secondary Tuberculosis <i>→ (Reinfection type) Adult type</i>
- This is tuberculous infection for the <u>first time</u>. - In Egypt it mainly affects children. - Spread of infection is more common. - Tissue destruction is less marked. - Lymph node infection more common. - Tissue reaction is slow. - Course of infection is mainly affected by innate immunity.	- This is tuberculous infection of sensitized individuals (previously infected with T.B) - In Egypt it mainly affects adults. - Spread of infection is less common (due to the presence of acquired immunity). - Tissue destruction is more marked (due to hypersensitivity). - Tissue reaction is accelerated. - Course of infection is determined by degrees of innate immunity, acquired immunity & hypersensitivity.

COMPLICATIONS OF TUBERCULOSIS: Common complications (regardless of the site):

- 1-Spread (see above)
- 2-Hemorrhage
- 3-Organ destruction and severe fibrosis
- 4-Amyloidosis (in chronic cases)
- 5-Recurrence (re-activation)

PRIMARY TUBERCULOSIS (CHILDHOOD TYPE)

Primary tuberculosis may develop in the lungs (due to inhalation of tubercle bacilli), in tonsils or intestine (due to ingestion of tubercle bacilli) or rarely in the skin (due to inoculation of the bacteria).

- In any of these organs, tubercle bacilli will exist in three sites:
 - 1-Somewhere in the infected organ (primary tuberculous focus)
 - 2-In the draining lymphatics (tuberculous lymphangitis).
 - 3-In the draining lymph nodes (tuberculous lymphadenitis).
 Existence of bacteria in these three sites is attributed to absence of acquired immunity (not yet developed) allowing some bacilli to be carried by macrophages and body fluids from the site of bacterial settlement to the draining lymphatics & lymph nodes.
- Therefore any primary tuberculous complex consists of tubercles in three sites:
 - a) Somewhere in the infected organ where the bacilli settle
 - b) In the draining lymphatics
 - c) In the draining lymph nodes.
- Fate of primary tuberculosis:
 - a) Localization (with possible later reactivation)
 - b) Spread (see before).

Microscopic → T.B. كل سؤال

Definition → *Inhalation*

I) PRIMARY PULMONARY TUBERCULOSIS

Aetiology: Inhalation of human tubercle bacilli.

Pathology: Primary Complex: *primary pulmonary complex* → *infection of Tuberculosis in Lung first*

1-Ghon's Focus: It is the initial tuberculous lung lesion:

Gross: A yellowish lesion; 1-2 cm in diameter, commonly subpleural. It occurs anywhere in the lung, but most frequent sites are the lower aspect of the upper lobe or the upper aspect of the lower lobe.

Microscopy: It consists of several adjacent caseating tubercles.

2-Tuberculous Lymphangitis: A chain of tubercles along the course of lymphatic vessels.

3-Tuberculous Lymphadenitis: The hilar lymph nodes are enlarged and show caseating tubercles. Caseation may be marked → matted nodes forming a "cold abscess".

Fate of primary pulmonary tuberculosis:

1-Localization and healing (fibrous replacement or capsulation), but living bacilli may persist within healed lesions.

2-Spread:

a) **Direct spread to:**

- Adjacent lung tissue → tuberculous pneumonia.
- Pleura → tuberculous pleurisy → exudative reaction → pleural effusion → later healing → dense fibrous adhesions.
- Pericardium (by direct spread from the hilar lymph nodes) → tuberculous pericarditis.

b) **Lymphatic spread:**

c) **Hematogenous:** As previously described, the effects depend on number of bacteria:

- 1- Small number → **No effect** (bacteria are destroyed by organs' phagocytic cells).
- 2- Moderate number → **Isolated organ tuberculosis** (one or few organs area affected)
- 3- Large number (usually after caseous destruction of vessels) → **Miliary tuberculosis:** The lungs, liver, kidneys, adrenals, serous membranes & other organs show huge numbers of small adjacent tuberculous lesions; 1-2 mm each. The condition is commonly fatal.

d) **Bronchial spread:** Caseous erosion of a bronchus from Ghon's focus of hilar lymph nodes → bronchial spread → distal bronchi and adjacent lung tissue → tuberculous bronchopneumonia. Coughing of infected sputum → affection of larynx, tonsils, etc.

3-Reactivation of capsulated or healed lesions (with persistent tubercle bacilli) may occur few years later if immunity is lowered, leading to secondary pulmonary tuberculosis (see later) and spread of infection (direct → tuberculous pneumonia, bronchial → larynx & tongue, blood → miliary or isolated organ T.B)

II) PRIMARY TUBERCULOSIS OF INTESTINE

Swallowing of human or bovine tubercle bacilli with dust or infected milk.

Pathology: Primary complex: *Primary Intestinal Complex*

1-The initial lesion usually appears in the terminal ileum and consists of a group of tubercles in the region of the Peyer's patches (where macrophages carry the bacilli to this area). The covering mucosa may undergo minimal ulceration.

2-Tuberculous Lymphangitis:

3-Tuberculous Lymphadenitis (mesenteric) The mesenteric lymph nodes are enlarged and show caseating tubercles. They may become matted → cold abscess.

Fate:

- 1-Localization. (Rare by fibrosis) *tuberc = severe disease*
- 2-Spread:
 - a) Direct and lymphatic: This leads to tuberculous peritonitis.
 - b) Hematogenous spread leading to isolated organ or miliary tuberculosis.

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* solitary polyp → Lymphoid collection in large intestine

It is more blessed to receive than to give.

Ques 1

Define: III) PRIMARY TUBERCULOSIS OF TONSILS

Aetiology: Infection of Tuberculosis in Tonsils 1st time
Swallowing of human or bovine tubercle bacilli.

Pathology: Primary complex: Primary Tonsils Complex

1-The initial lesion is a small focus composed of tubercles. The covering mucosa of tonsil may ulcerate.

2-Tuberculous lymphangitis.

3-Tuberculous lymphadenitis of the cervical lymph nodes which become enlarged & show caseating tubercles. [Matting may occur & a cold abscess may develop] The overlying skin may develop tuberculous sinuses

Fate: 1-Localization. 2-Spread.

Ques 2

IV) PRIMARY TUBERCULOSIS OF SKIN (rare)

Define + Microscopic

Tubercle bacilli inoculated through a skin abrasion lead to a primary complex, which may localize or spread.

TUBERCULOUS LYMPHADENITIS

VIP

As shown before, tuberculous lymphadenitis occurs as a part of primary complex. The hilar lymph nodes are affected in case of primary pulmonary T.B, the cervical nodes in case of primary T.B of tonsils & the mesenteric nodes in case of primary intestinal T.B.

Gross Features: The affected nodes are enlarged, first discrete, then may become matted and soft due to marked caseation → Cold Abscess

Microscopy: Tubercles

Fate & Complications:

1-Localization

2-Spread

a) Direct from cervical lymph nodes → cervical skin sinus formation, from hilar nodes → tuberculous pericarditis and from mesenteric nodes → tuberculous peritonitis.

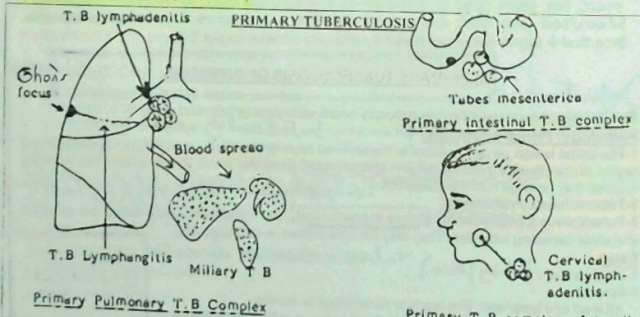
b) Lymphatic spread to other lymph nodes.

c) Blood spread causing isolated organ or miliary tuberculosis.

d) Bronchial spread due to bronchial erosion from hilar nodes in case of pulmonary tuberculosis.

3-Reactivation (if immunity is lowered)

Definition = Inflammation T.B of Lymph node



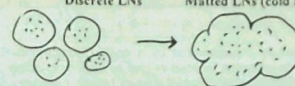
Pyogenic abscess
Puss

Cold abscess
Caseous material
في الرقبة
Cold abscess

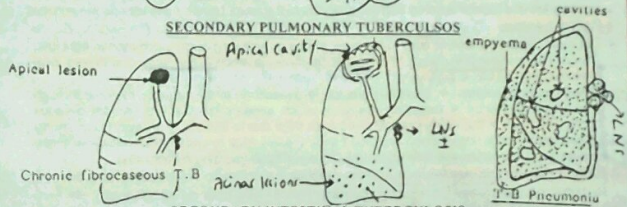
+

TUBERCULOUS LYMPHADENITIS

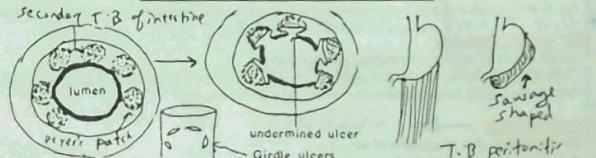
Discrete LNs Matted LNs (cold abscess)



SECONDARY PULMONARY TUBERCULOSIS



SECONDARY INTESTINAL TUBERCULOSIS



SECONDARY (REINFECTION) TUBERCULOSIS (ADULTHOOD TYPE)

This is tuberculosis in persons that have had a previous primary exposure to tuberculosis. It may be due to one of two possibilities:

- 1-New exogenous infection (inhalation, ingestion).
- 2-Reactivation of dormant living tubercle bacilli within a healed primary tuberculous lesion.

II) SECONDARY PULMONARY TUBERCULOSIS

Aetiology:

- 1-Inhalation of human tubercle bacilli (exogenous route) more common in adult
- 2-Reactivation of healed or capsulated Ghon's focus containing living tubercle bacilli.

Course of infection: Disease severity depends on dose and virulence of bacteria, degree of immunity & hypersensitivity. The lesions may be

- a) Minimal and undergo fibrosis (regressive lesion)
- b) Progressive disease of two main forms (see table):

Chronic Fibrocaseous Pulmonary Tuberculosis	Acute Caseous Bronchopneumonia
Occurs in patients with moderate levels of immunity and hypersensitivity.	One or more of the following factors:
Slow chronic course.	1) Large dose of virulent bacteria
	2) High hypersensitivity
	3) Low immunity
	Acute fatal course.

acinar = pap + acinus

Give account on chronic fibro caseous pulmonary tuberculosis

A) CHRONIC FIBROCASEOUS TUBERCULOSIS (CAVITARY TUBERCULOSIS)

* Definition + Aetiology → Def + Act

* Pathology: This type of tuberculosis is essentially characterized by a cavity (or sometimes more than one cavity), most commonly (but not necessarily) located in one or both lung apices, associated with secondary lesions (acinar lesions) due to transbronchial spread. Lymph node lesions are minimal.

1-**Apical Lesion:** In Apex → Less blood supply → Less local resistance (less blood supply). In most cases, the lesions start in the apex of one or both lungs (more common in right lung which has a wider bronchus). It is said to be more common in the apex due to less local resistance (less blood supply).

Progressive caseation → bronchial erosion → evacuation of the caseous material through the eroded bronchus → formation of a cavity which appears irregular with shaggy caseous lining. The wall of this cavity gradually becomes thick due to fibrosis. The cavity is commonly traversed by thick ridges which represent thick vessels (due to endarteritis). However these vessels may be destroyed leading to severe hemorrhage (causing hemoptysis).

2-**Basal Lesions (acinar lesions):** Small caseous foci occurring in the base of lung due to transbronchial spread following caseous bronchial erosion from the apical lesion.

3-**Insignificant Lesions within the hilar lymph nodes:** Lymphatic spread is uncommon due to the presence of acquired immunity (the lymphokine MIF inhibits migration of macrophages).

* **Rare Tubercle lymphadenitis due to MIF**

* **Microscopic Features:**

1-Large areas of caseous necrosis, surrounded by;
2-Fibrosis & scattered tubercles (epithelioid cells, Langhan's giant cells & lymphocytes).
3-Adjacent vessels show endarteritis. Hemorrhage is common.

* **Complications:**

1-Hemoptysis, due to erosion of vessels.
2-Rupture of the cavity into the pleural sac results in pneumothorax.
3-Spread of infection (relatively less common than primary T.B):

a) Direct leading to:
i) tuberculous pleurisy or tuberculous empyema (caseous material fills the pleural sac),
ii) tuberculous pericarditis and mediastinitis.
b) Blood spread leading to isolated organ tuberculosis or miliary tuberculosis.
c) Bronchial spread:
i) Coughing of infected sputum may lead to tuberculosis of larynx, tonsils, tongue.
ii) Swallowing of this sputum causes secondary intestinal tuberculosis.
d) Lymphatic spread: Uncommon.

4-Right-sided heart failure may develop due to bilateral lung fibrosis (in bilateral cases).

5-Secondary amyloidosis (reactive systemic amyloidosis).

* **Clinical Features (signs & symptoms):** Due to tissue destruction & accompanying toxemia:
1-Weight loss, anemia, pallor, fever and sweating. light fever + light sweating
2-Chest pain & dyspnea + cough
3-Hemoptysis
4-Pleural effusion

B) ACUTE TUBERCULOUS BRONCHOPNEUMONIA

This rare type occurs when one or usually more than one of three factors exist (large dose of virulent bacteria, low immunity or high hypersensitivity).

Gross Features:

1-The affected lung shows multiple caseous foci around the bronchioles (bronchopneumonia) that rapidly progress leading to caseous consolidation of almost the

Any 2nd T.B. less spread but more destructive
Miliary T.B. more common in 1st T.B.

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Angulus @ edge
@ shape
@ floor
@ base

whole lung (tuberculous pneumonia). Focal liquefaction of the caseous material leads to small irregular cavities. The pleura shows tuberculous empyema.
2-The hilar lymph nodes are enlarged and caseous.

Microscopic Features:

Extensive caseation, few epithelioid cells, few Langhan's giant cells and no fibrosis.

Fate: Rapidly fatal. Miliary tuberculosis is common → no gross caseation = less destruction

II) SECONDARY TUBERCULOSIS OF INTESTINE

Cause: Usually due to ingestion of infected sputum in patients with chronic fibrocaseous pulmonary tuberculosis.

Pathological Features:

1-The lesions develop mainly in the terminal ileum and adjacent caecum. The bacilli reach the Peyer's patches (and solitary follicles of caecum) → caseous necrosis and erosion of the covering mucosa → tuberculous ulcers which are characterized by:

- Multiple
- Edges are ragged and undermined.
- Ulcer floor is yellowish, caseous
- In the terminal ileum they are transversely arranged (girdle ulcers) since the affected Peyer's patches are anatomically arranged in the form of transverse arcs.
- They heal by fibrosis.

2-The mesenteric lymph nodes show minimal lesions.

Complications:

- 1-Intestinal Hemorrhage → above the caecum → melena → not bleeding infection → all
- 2-Intestinal fistulae → ileo colic
- 3-Perforation of the ulcers leads to septic peritonitis.
- 4-Spread of infection:
a) Direct and Lymphatic → tuberculous peritonitis.
b) Blood spread → isolated organ or miliary tuberculosis.
- 5-Fibrosis → intestinal obstruction.
- 6-Secondary amyloidosis.

III) SECONDARY TUBERCULOSIS OF TONSILS

It is usually caused by spread of tubercle bacilli through infected sputum. A tuberculous ulcer with undermined edges develops.

IV) SECONDARY TUBERCULOSIS OF SKIN

There are several patterns but the most common type is Lupus Vulgaris.

LUPUS VULGARIS:

- The mode of infection is not apparent, however it is suspected to be due to blood spread (e.g. from pulmonary tuberculosis) but it may also possibly due to exogenous infection of sensitized individuals.
- The skin of face and neck is the most commonly affected site (more than 90% of cases).
- The skin shows nodules and ulcers with undermined edges.
- The lesions are precancerous.

Lupus erythematosus
Lupus vulgaris → 2 Lupus vulgaris

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White Knightlane

ORGAN TUBERCULOSIS DUE TO SPREAD OF INFECTION

Pulmonary, intestinal, tonsillar & skin tuberculosis can occur as primary or secondary disease. However spread in either primary or secondary tuberculosis can lead to affection of any organ.

I) TUBERCULOSIS OF HEART & PERICARDIUM

1-Tuberculous pericarditis (myocarditis, pericarditis & endocarditis) is rare and may occur as a part of miliary tuberculosis.

2-Tuberculous pericarditis: May be due to spread from mediastinal lymph nodes in cases of pulmonary T.B. The pericardial sac shows an exudative reaction, caseation and later fibrosis. Severe fibrosis may lead to serious constrictive pericarditis interfering with the diastolic expansion of the heart and constricting the orifices of the venae cava leading to generalized venous congestion.

II) TUBERCULOUS PERITONITIS

Aetiology: Direct spread from intestinal tuberculosis, tuberculous mesenteric lymph nodes or from tuberculous salpingitis. **2-Lymphatic and blood spread** from distant organs as lungs is less common.

Pathology: Several forms (according to infection dose, degree of immunity and hypersensitivity), the most common forms include:

1-Wet or ascitic type of tuberculous peritonitis: (wet)

The peritoneal cavity is distended with a large amount of serous exudate rich in lymphocytes, poor in epithelioid cells (exudative reaction).

2-The dry or adhesive type of tuberculous peritonitis: There is little fluid exudate, many tubercles & progressive marked fibrosis (frozen abdomen). Fibrosis may lead to:
 • Fibrosis of the **greater omentum** leads to **sausage-shaped** mass across the upper abdomen, since the omentum gets rolled on itself.
 • Fibrous adhesions between loops of intestine.

Complications:

- 1-Intestinal obstruction due to adhesions.
- 2-Intestinal fistulae.

III) GENITOURINARY TUBERCULOSIS

TUBERCULOSIS OF KIDNEY

May be: 1) Part of generalized miliary tuberculosis 2) An isolated form (chronic renal tuberculosis)

CHRONIC RENAL TUBERCULOSIS:

Aetiology: Tubercle bacilli reach one or both kidneys through:

- 1-Blood spread from distant organs.
- 2-Ascending spread from tuberculosis of urinary bladder.

Pathological Features:

- Tuberculous lesions start at the **apex or base of pyramids** **most blood supplied area**.
- Progressive caseation → **corticomedullary destruction**.
- Evacuation of caseous material through calyces → **irregular tuberculous cavities**.
- The walls of the cavities undergo progressive fibrosis.
- Tuberculous pyonephrosis may occur. This is distension of the pelvis and calyces with retained caseous material. It occurs if pelviureteric fibrosis occurs → obstruction.
- Small (contracted) kidney may occur due to fibrosis of corticomedullary lesions.

* **Bilaterally Infection** because mostly ¹³⁴
 Aetiology due to blood
 & both have common arterial supply

Complications:

- 1-Hematuria
- 2-Spread of infection:
 a) **Descending spread** → ureter & bladder → **ascending spread** to the other kidney may occur.
 b) **Blood spread** → isolated organ or miliary tuberculosis.
- 3-Complications of chronic renal disease:
 a) Hypertension
 b) Chronic renal failure, bc cause both kidneys → ↑ Renin from JGA
- 4-Amyloidosis

TUBERCULOSIS OF URINARY BLADDER

Aetiology:

- 1-Descending spread from renal tuberculosis, or direct spread from tuberculosis of prostate, seminal vesicles
- 2-Blood spread from tuberculosis of distant organs or fallopian tubes.

Pathology: Tuberculous ulcers with undermined edges, then fibrosis.

Complications:

- 1-Hematuria
- 2-Spread of infection:
 a) Ascending to kidneys.
 b) Blood spread.
- 3-Fibrosis may be extensive leading to a contracted bladder (thumb-sized bladder).

TUBERCULOSIS OF THE EPIDIDYMIS

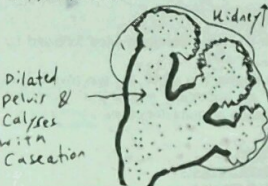
It is usually blood-borne, caseous necrosis of the epididymis may involve skin of the posterior aspect of scrotum leading to sinus formation. Direct spread to the testis leads to tuberculous orchitis and fibrosis which in bilateral cases leads to infertility + complications.

TUBERCULOSIS OF THE FALLOPIAN TUBES (Tuberculous Salpingitis)

Infection is often bilateral and is usually blood-borne. The tubes show tubercles and may become distended with caseous material (tuberculous pyosalpinx), followed by tubal fibrosis. Spread may lead to tuberculous peritonitis and tuberculous endometritis. Bilateral tubal fibrosis may lead to infertility.

GENITOURINARY TUBERCULOSIS

T.B pyonephrosis



TUBERCULOSIS OF NERVOUS SYSTEM

T.B epididymitis

Sinus

Testis

Bilateral T.B Pyosalpinx

Tuberculosis

B. epididymis	Syphilis
sterile sinus	in body of Testis
scrotum	

@ back	@ back of the	@ back of scrotum	@ back of Breast
--------	---------------	-------------------	------------------

HCG + 580
 * mostly in large joint at low age
 (V) TUBERCULOSIS OF JOINTS (Tuberculous Arthritis)

Aetiology:

- 1- Blood borne infection.
- 2- Direct spread from tuberculosis of adjacent bone.

Pathological Features (Tuberculous arthritis):

- Age: most common before the age of 25 years.
- Sites: Hip and Knee are the most common sites.
- The synovium shows tubercles and undergoes progressive fibrosis.
- Joint effusion may occur.
- Pannus: This is creeping of granulation tissue (from the synovium) under the articular cartilage → fragmentation of cartilage → exposure of both bony ends → fibrous union (fibrous ankylosis) → fibrosis of joint
- Direct spread of infection → destruction of ligaments.
- Spread to periarticular soft tissues → cold abscess formation & multiple skin sinuses.

Complications:

- 1- Spread of infection (direct and by blood).
- 2- Fibrous ankylosis.
- 3- Hemorrhage (hemarthrosis)
- 4- Amyloidosis

(VI) TUBERCULOSIS OF BONE (Tuberculous Osteomyelitis)

Source of infection: Usually blood-borne

Pathological features:

- 1- Caseous necrosis & bone destruction (tuberculous caries) → complete
- 2- Inadequate callus formation (poor healing).
- Sites: Most common in vertebrae and ends of long bones.
- 1- Ends of long bones: Tuberculous lesions start in the metaphysis then spread leading to subperiosteal cold abscess. Direct spread to nearby joints leads to tuberculous arthritis.
- 2- Flat bones as ribs & pelvis. This is rare. A subperiosteal cold abscess develops.
- 3- Short bones of hands or feet (tuberculous dactylitis): This is rare. The fingers or toes appear fusiform.
- 4- Vertebrae (Pott's disease).

TUBERCULOSIS OF VERTEBRAE (POTT'S DISEASE)

Aetiology:

- 1- Blood borne infection.

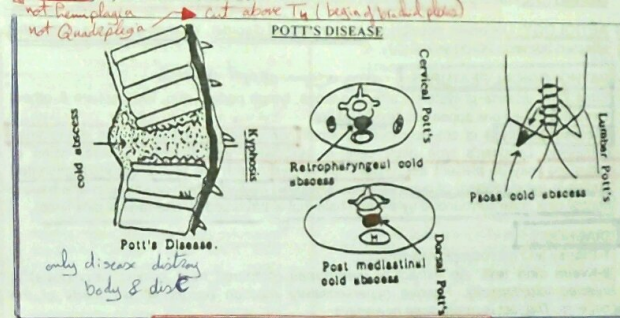
Pathological Features:

- The lower thoracic & upper lumbar vertebrae are the most common sites followed by cervical vertebrae.
- Two or more adjacent vertebrae as well as the intervening discs are destroyed. It is worth noting that destruction of the discs is an important radiological sign that distinguishes Pott's disease from metastases. In case of metastases the vertebrae are destroyed, while the discs are spared.
- Pott's disease is characterized by three main features:
 - 1- Kyphosis due to anterior collapse of the destroyed vertebrae.
 - 2- Cold abscess: It consists of a squeezed caseous material.

Pott's disease is in cervical & thoracic

- a) In the cervical region, the abscess acquires a retropharyngeal position. It may appear at the posterior border of sternomastoid and may sometimes reach the axilla.
- b) In the thoracic region the abscess appears in the posterior mediastinum.
- c) In case of lumbar Pott's disease, the cold abscess may appear in the lumbosacral triangle. The caseous material may reach the psoas sheath and appear in the femoral triangle (Psoas cold abscess).

- 3- Paraplegia develops in about 10% of cases due to spinal cord compression, ischaemia (caused by endarteritis obliterans and sometimes thrombosis) or traumatic cord injury by fractured vertebrae.



(VII) TUBERCULOSIS OF NERVOUS SYSTEM

TUBERCULOMA

This is a mass of caseation surrounded by gliosis occurring in the brain or spinal cord. It may lead to increased intracranial tension and may be clinically and radiologically mistaken for a tumor.

TUBERCULOUS MENINGITIS

Aetiology: Blood-borne infection.

Pathological Features:

- 1- Tubercle bacilli are mainly localized in the pia-arachnoid membranes & within the lining of the ventricles → tubercles and exudative reaction.
- 2- Arteries of the subarachnoid space often show softening.
- 3- The cerebrospinal fluid is characterized by:
 - a) Increased tension
 - b) Increased protein content
 - c) Sugar and chloride contents are decreased.
 - d) A large number of lymphocytes.
 - e) Tubercle bacilli may be detected.

Complications:

- 1- Spread:
 - a) Direct leading to tuberculous encephalitis
 - b) Blood spread.
- 2- Fibrosis leads to:
 - a) Hydrocephalus due to obstruction of CSF flow. only in children
 - b) Cranial nerve paralysis due to compression.
- 3- Infarcts due to endarteritis and thrombosis.

@ Hemorrhage

meningitis is diagnosed by Lumbar puncture between L3-L4

T.B * Caseation * Culture +ve	Atypical Mycobact * pus abs * suppurative change	Sarcoidosis * non caseating * Tubercle abs
-------------------------------------	--	--

MCQ + Complete
صرا لا اطفال غالباً

ATYPICAL MYCOBACTERIOSIS

Atypical mycobacteria are a common cause of granulomatous lymphadenitis, particularly in children. They may also affect lungs, intestine, skin and other sites. The lesions are microscopically indistinguishable from those of tuberculosis, however associated suppurative changes are common. The diagnosis primarily depends on culture characteristics.

SARCOIDOSIS

DEFINITION: This is a systemic disorder, characterized by tubercle-like non-caseating granulomas.

AETIOLOGY: Uncertain, possibly an immunological disorder. Women are more commonly affected between 20-30 years.

PATHOLOGICAL FEATURES:

Sites: The disease is systemic affecting lungs, lymph nodes, skin, liver, spleen & others. **Grossly:** the lesions appear as small nodules.

Microscopically: It is characterized by small noncaseating epithelioid cell granulomas containing Langhan's type giant cells & associated with fibrosis. Several types of inclusions may be present as Schaumann bodies (which are round, calcified laminated bodies in the cytoplasm of giant cells) and Asteroid bodies (which are smaller and have a central pink zone surrounded by a clean halo that is traversed by fine radial pink lines).

DIAGNOSIS:

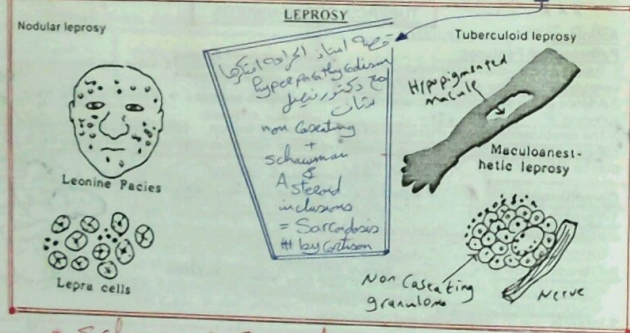
1-Biopsy and microscopic examination.
2-Kveim skin test: An extract of granulomas (prepared from splenic sarcoidosis) is injected intradermally. Positive hypersensitivity reaction occurs in two thirds of the patients. The test is rarely done nowadays.

3-Angiotensin converting enzyme are secreted by cells in the granuloma. Detection of elevated levels of this enzyme in serum helps the diagnosis of sarcoidosis.

4-Culture of tissue. Wite peptide solution

COURSE (FATE):

1-About 65% of patients undergo spontaneous remission. Steroids are helpful in treatment.
2-Death may occur due to pulmonary fibrosis or secondary infection & nephrocalcinosis



- * Schaumann → Sarcoidosis
- * Councilman → Apoptosis p. 39
- * Kusselman → Bronchial Asthma

كما لا يغفلوا كل الممرات المبرم
من الموت
الامر كان حرجاً فنياً في الولد

LEPROSY

Definition: Infective granulomatous disease caused by *Mycobacterium leprae*. *Culture organism*

Aetiology: The mode of transmission of *Mycobacterium leprae* (lepra bacilli) is thought to be through nasal mucosa (inhalation) or through skin abrasions, after prolonged contact with a patient. Incubation period is very long, up to several years.

Types: The mildest form of leprosy is called **tuberculoid** leprosy (in patients with high resistance). The severest form is called **lepromatous** leprosy (little resistance). Grades between tuberculoid and lepromatous types are called **borderline** leprosy.

1- LEPROMATOUS LEPROSY (Nodular Leprosy)	2- TUBERCULOID LEPROSY (Maculo-anesthetic Leprosy)
- This is the severest form of leprosy. The patient's resistance is low. There is a defect in T lymphocytes which are not stimulated by the lepra bacilli & consequently, these T cells do not instruct the macrophages to destroy the phagocytized bacilli. - The tissue reaction is called leproma. It consists of large numbers of macrophages with pale foamy cytoplasm (bacterial lipids). These foam cells contain large numbers of rapidly multiplying bacilli. Partial lysis of the walls of these bacilli results in the foam appearance of the cells (lysis is not complete due to defective digestion). These foam cells are called lepra cells. Lesions of lepromatous leprosy include: 1-Skin lesions: These lesions may be macular (hypopigmented patches), diffuse or nodular (commonest). Skin nodules develop most commonly in skin of face and extremities. In the face, these nodules are associated with loss of eye brows and eye lashes resulting in leonine facies. Ulceration and secondary infection of these nodules is common. 2-Mucous (nasal) lesions: Nasal mucosal nodules may develop causing nasal obstruction. 3-Neural Lesions: Thickening & destruction of large peripheral nerves as ulnar, facial, etc. These occur late (peroneal nerve). 3-Trophic Lesions: Loss of sensation → ulcerations & deformities of the hands & feet. 4-Visceral Lesions: The liver, testis, lymph nodes, eyes and other sites may be infected by lepra bacilli.	- This is the mildest form of leprosy occurring in patients with adequate immunity. <i>Non Caseating</i> - The tissue reaction consists of noncaseating granulomas composed of epithelioid cells, giant cells and lymphocytes. They differ from sarcoidosis in: 1-Few lepra bacilli may be detected (by the Ziehl-Neelsen stain). 2-The tuberculoid granulomas occur along side nerves associated with nerve destruction. Lesions of Tuberculoid Leprosy include: 1-Skin Lesions: A single or few hypopigmented skin macules with impaired sensation (anesthetic) and impaired sweating. 2-Neural Lesions: Peripheral nerve thickening. Neural involvement occurs early. 3-Trophic lesions: Same as lepromatous.

- * no caseation in both cases
- * nodular has more bacilli lepra more than Tuberculoid lepra
- * nodular mostly in skin face (large blood supply)

العدوى (eye brows) & lepra disease
Mushroom

من مميزات (سيفيليس)
 ١- انتقاله عن طريق الاتصال الجنسي
 ٢- انتقاله عن طريق الدم
 ٣- انتقاله عن طريق الحشرات
 ٤- انتقاله عن طريق الثدييات
 ٥- انتقاله عن طريق الحشرات
 ٦- انتقاله عن طريق الثدييات
 ٧- انتقاله عن طريق الحشرات
 ٨- انتقاله عن طريق الثدييات
 ٩- انتقاله عن طريق الحشرات
 ١٠- انتقاله عن طريق الثدييات

SYPHILIS

Definition: Syphilis is an infective disease caused by *Treponema pallidum* spirochaetes

Aetiology & Mode of Infection: The spirochaetes can be transmitted in one of 2 ways:

Acquired Syphilis:

- Veneral Type (most common). Bacteria are transmitted by sexual contact
- Non-veneral type: 1) Touching syphilitic lesions. 2) Blood transfusion from syphilitic donor.

Congenital Syphilis: Transplacental transmission from syphilitic mother to her fetus.

Syphilitic Tissue Reaction

Syphilis is characterized by:

- Progressive, endarteritis obliterans. = severe early
- Chronic proliferative inflammatory reaction, rich in plasma cells, poor in fluid exudate.
- Granulation tissue and fibrosis
- Considerable necrosis mainly in gummatous lesions of the tertiary stage.

A) ACQUIRED SYPHILIS (The Venereal Type)

Spirochaetes are among the most invasive organisms. Once they infect the body (during sexual intercourse or kissing), they are rapidly disseminated by lymphatics & blood before any lesions can be detected. It is divided into 3 stages. The primary and secondary stages are infective (particularly the second stage), but are curable by antibiotics, while in the tertiary stage, only very few (if any) spirochaetes survive and the lesions are destructive & irreversible caused by marked necrosis & fibrosis. Necrosis is due to hypersensitivity as well as ischaemia caused by severe endarteritis.

a) Primary stage; about 2-6 weeks (incubation period) after the onset of infection.

b) Secondary stage; about 2 months after healing of the primary stage.

c) Tertiary stage (in one third of untreated cases); after 2-10 years from the secondary stage.

I- PRIMARY SYPHILIS (CHANCER)

Onset: Lesion appears at site of infection, 2-6 weeks after infection. It is called chancre or hard sore.

Sites of chancre

- Genitalia: penis, vulva, vagina, cervix.
- Extragenital: lips, tongue, nipple and anus (in homosexuals).

Gross:

1-A hard painless small papule, which ulcerates. The lesion is highly infective. The ulcer heals by minimal fibrosis → thin scar

2-The regional lymph nodes are enlarged and discrete

Microscopy: Syphilitic reaction (see above)

II- SECONDARY SYPHILIS

Onset: Two months after the primary stage. It is the most infective stage

Gross Features: The following lesions develop:

1-Skin lesions: due to endarteritis obliterans

- Skin rash: A generalized painless skin rash all over the body. It consists of red macules (flat

- patches, red papules (small raised lesions) & yellowish pustules (secondary infected papules)
- Condyloma latum: A large raised cutaneous swelling occurring in moist areas as vulva & axilla.
- Other lesions as alopecia (loss of scalp hair) & leukoderma.

2-Mucus patches develop in oropharyngeal, anal or vaginal mucosa. These patches may ulcerate → small adherent ulcers (snail track ulcer).

3-Generalized lymph node enlargement (sometimes with splenic enlargement)

Microscopic picture: Syphilitic reaction

III- TERTIARY SYPHILIS

Onset: 2-10 years after healing of the lesions of the secondary stage.

Pathology: Any organ may be affected. Lesions are destructive & include two types

1-Gumma (Localized Affection)

Gross Picture: Single or multiple. It can occur in several sites. It is a circumscribed pale yellowish gray rubbery mass, variable in size.

Microscopic Picture: Gumma consists of central necrosis surrounded by syphilitic inflammatory reaction and fibrosis.

2-Diffuse Syphilitic Inflammation:

Grossly: The affected organ or tissue appears firm grayish and fibrotic.

Microscopically: Minimal scattered foci of necrosis, associated with diffuse syphilitic reaction and fibrosis.

Organ Pathology In Tertiary Syphilis: ulcer only not carcinoma while T.B. is cancer & could

1-Syphilis of skin: Gumma → ulceration → gummatous ulcer characterized by punched out edges (sharp deep edges), smooth floor, serpiginous irregular margins & indurated base (due to fibrosis).

2-Syphilis of digestive system: Any part can be affected:

a) Tongue: One of two forms, both predispose to tongue cancer.

- Gumma → ulcer
- Diffuse inflammation → thickening and leukoplakia

Remark: Tongue may be affected in all three stages of syphilis:

- Primary stage: chancre
- Secondary stage: mucus patches, snail track ulcer
- Tertiary stage: gumma or diffuse

b) Liver: One are usually multiple gummata surrounded by fibrosis → pseudolobulation of the liver (hepar lobatum)

3-Syphilis of Cardiovascular System:

a) Heart: It may occur as pancarditis or localized affection. Gumma of the interventricular septum → heart block

b) Arteries: Any artery can be affected by diffuse syphilitic inflammation (syphilitic arteritis)

Syphilitic Aortitis commonly affects the thoracic aorta. The vasa vasorum shows end arteritis, associated with syphilitic inflammatory reaction and fibrosis leading to the following effects and complications

- Aortic incompetence due to dilatation of the weakened fibrotic aortic ring & retraction of the fibrotic cusps → left ventricular failure (see systemic pathology).
- Stenosis of coronary orifices → ischaemia.
- Aortic aneurysm: It is due to dilatation of the weak fibrotic aortic wall. It may affect part of the circumference (saccular aneurysm) or the whole circumference of the affected aortic segment (fusiform aneurysm). It may be complicated by thrombosis, pressure effects on the surroundings (as oesophagus and vertebrae) or rupture leading to fatal hemorrhage

It is more blessed to give than to receive.

4-**Syphilis of Respiratory System:** Can effect any part leading to several effects as laryngeal stenosis, tracheal & bronchial stenosis and lung destruction

* 5-Syphilis of Bones:

- Diffuse syphilitic inflammation of long bones leading to bone thickening (osteosclerosis).
- Gumma of flat bones → Skull destruction → worm eaten appearance.
- Nasal septum destruction → saddle nose.
- Hard palate destruction → perforation.

6- Syphilis of Joints:

- Gummatous or diffuse affection may be associated with effusion (hydrarthrosis).
- Charcot's joint (see tabes dorsalis in neurosyphilis).

7-**Syphilis of Testis:** The testis is enlarged with loss of sensation. Gumma may ulcerate anteriorly through scrotal skin.

* 8- Neurosyphilis: Develops late in tertiary stage in 2% of patients:

a) Meningovascular syphilis:

- Syphilitic arteritis of cerebral or spinal arteries.
- Syphilitic meningitis → meningeal fibrosis → hydrocephalus and compression of nerve roots leading to neural paralysis.

b) Parenchymatous syphilis (usually accompanied by syphilitic meningitis) includes:

- Tabes dorsalis: There is selective destruction of posterior columns of spinal cord, followed by gliosis. The posterior nerve roots also destroyed by syphilitic inflammation → loss of sensations → trophic ulcers and Charcot's joint (osteoarthritis).

* General paralysis of insane: Diffuse cerebral affection → brain atrophy & ventricular dilatation

(GPI)

B) CONGENITAL SYPHILIS

Aetiology: It is due to transplacental infection from a syphilitic mother to her fetus.

Pathological Features:

The placenta is enlarged and pale. Microscopically it shows end arteritis and chorionic villitis (characterized by exudation of plasma cells and lymphocytes).

The clinical possibilities include:

- Abortion or stillbirth.
- The baby survives and develops two groups of lesions:

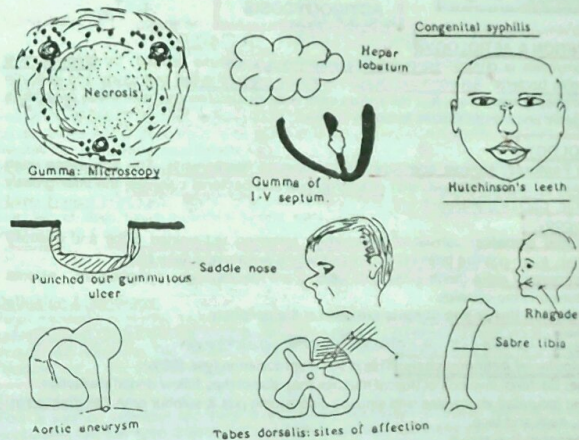
a) **Early Manifestations:** These develop during the first two years of life (often between the 2nd & 10th weeks). These lesions largely resemble those of the 2nd stage of acquired syphilis.

- Skin rash and condylomata.
- Mucous patches.
- Generalized lymph node enlargement.
- Rhagades: Radiating scars at the angles of mouth and anus.
- Syphilitic inflammation of organs, resulting in:
 - Pneumonia alba: pale lungs showing syphilitic inflammation.
 - Syphilitic cirrhosis.
- Syphilitic epiphysitis (syphilitic osteochondritis) → retardation of bone growth.

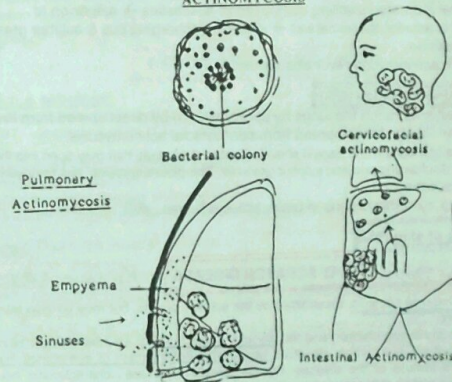
b) Late Manifestations (2-30 years):

- Hutchinson's Teeth: The permanent central incisors are short, notched & widely separated.
- Deafness due to affection of 8th cranial nerves.
- Eye: Keratitis, iritis, retinitis.
- Saber tibia (Sword tibia): The tibia is thickened and bent.
- Gumma of palate (perforation) and nose (saddle nose).
- Neurosyphilis.

SYPHILIS



ACTINOMYCOSIS



- 2-GIT Candidiasis: Most common in oesophagus, particularly in AIDS.
 3-Invasive (disseminated) Candidiasis: It is due to blood spread. **It is often fatal**. The manifestations include:
 a) Microabscesses affecting lungs, liver, kidneys, brain, myocardium... etc.
 b) Endocarditis. c) Meningitis. d) Endophthalmitis.

HISTOPLASMOSIS

The disease is caused by inhalation of *Histoplasma capsulatum* fungus which exists in the excreta of birds & bats. The disease is most common in the Mississippi valley in USA. The lungs and hilar lymph nodes are affected causing pneumonia or sometimes cavity lesions resembling tuberculosis. Blood dissemination may occur (fatal).

ASPERGILLOSIS

There are many species of this fungus, but *Aspergillus fumigatus* is the most common human pathogen. It is commonly an opportunistic lung infection. There are three types of pulmonary aspergillosis:

- 1-Allergic bronchopulmonary aspergillosis: Caused by an allergic inflammatory reaction due to repeated inhalation of fungal spores.
- 2-Aspergilloma: This is colonization of the fungus in a pre-existing lesion commonly tuberculous cavity or bronchiectasis.
- 3-Invasive aspergillosis: May occur in immunocompromised patients. The fungus spores germinate and produce hyphae that directly spread through bronchi and lung and can reach blood causing thrombosis.

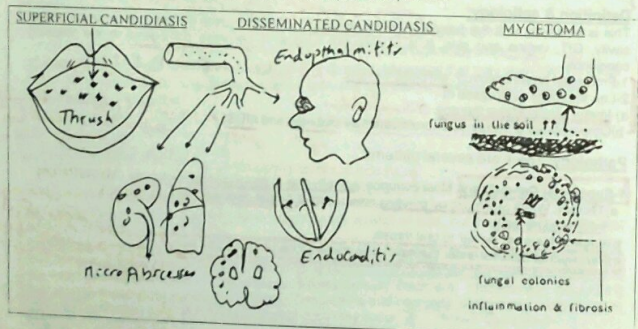
CRYPTOCOCCOSIS

The fungus *Cryptococcus neoformans* exists in pigeon droppings and is transmitted to man by inhalation. It is a systemic disease with high predilection to lungs and meninges.

COCCIDIODOMYCOSIS

The fungus *Coccidioides immitis* exists in soil in some areas of the world. It is a chronic necrotizing disease that may clinically and pathologically resemble tuberculosis. The disease may be:

- 1-Mild asymptomatic disease limited to lungs and regional LNs. This is the most common form.
- 2-Disseminated coccidioidomycosis in immunocompromised patients.



CHAPTER XII

VIRAL INFECTIONS

Definition: Viruses are the smallest microorganisms (often 20-30 nm in size). They are obligate intracellular agents that depend on the host metabolic machinery for their replication. A single virus (virion) consists of a core of nucleic acid and a protein coat (capsid). Viruses are classified according to the type of nucleic acid they contain into either DNA or RNA viruses.

Mode of infection varies according to type of virus. Viruses may infect man by

- 1-Inhalation as influenza virus.
- 2-Ingestion as hepatitis A virus and poliovirus.
- 3-Through blood (injection) as hepatitis B & C viruses.
- 4-Sexual transmission as HIV → AIDS.
- 5-Inoculation e.g. trachoma virus.
- 6-Bites of vectors e.g. yellow fever transmitted by bites of the mosquito *Aedes aegypti*.

Clinical forms of viral infections:

- 1-Asymptomatic infections that go unrecognized.
- 2-Acute illness e.g. influenza, mumps, measles, acute hepatitis.
- 3-Chronic illness with or without a preceding phase of acute illness e.g. chronic hepatitis & AIDS.
- 4-Carrier state with a potential for disease activation as some cases of hepatitis.
- 5-Oncogenic viruses can cause neoplastic disease (e.g. papilloma virus).

Remark: A single virus can produce different clinical effects depending on resistance & age of the patient (e.g. VZ & CMV). On the other hand several viruses can produce the same pathological features (e.g. influenza viruses).

Mechanism of virus-induced cell injury:

- 1-Interference with cellular synthesis of DNA or RNA.
- 2-Cell membrane injury (as HIV).
- 3-Cell lysis (as in influenza).
- 4-Hypersensitivity host reactions (as in chronic hepatitis).

Tissue reaction to viruses:

- 1-Cell changes:
 - a) Viruses infect cells & may form intracellular inclusion bodies (cytoplasmic or nuclear).
 - b) Viruses may infect specific cells (e.g. hepatitis viruses infect hepatocytes), but some viruses are systemic, infecting many cell types (e.g. CMV).
 - c) The tissue reaction is variable:
 - There may be no reaction at all as in latent viral infections.
 - Cell degeneration & Necrosis (as in hepatitis viruses & poliovirus).
 - Cell proliferation (as in case of papilloma virus).

2-Inflammation: Lymphocytes and macrophages are the 2 most important inflammatory cells.

- Examples of virus infections:** HAV (hepatitis A virus), HBV (hepatitis B virus), HCV (hepatitis C virus), HIV (Human Immunodeficiency Virus), EBV (Epstein Barr Virus), HPV (Human Papilloma Virus), CMV (Cytomegalovirus) & others (see below).

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) HIV

Definition: AIDS is a disease caused by HIV that leads to marked immunosuppression.

Aetiology: AIDS is a world-wide disease, but uncommon in Egypt. The causative virus is called HIV (human immunodeficiency virus). It is an RNA virus that mainly affects CD4+ cells (T helper cells) → marked loss of CD4+ cells and marked impairment of the function of the remaining surviving cells. The monocytes and macrophages are also significantly affected. There are 2 related forms of the virus called HIV-1 and HIV-2.

The effects of suppression and loss of CD4+ cells can be summarized as follows:

- 1- Decreased response to antigens and decreased lymphokine secretion.
- 2- Reduction of the specific cytotoxic action of CD8 cells.
- 3- The NK cells become less capable of killing tumor cells.
- 4- B cells/Plasma cells show depressed immunoglobulin production in response to antigens.
- 5- Disordered macrophage functions:
 - a) Diminished cytotoxic/phagocytic ability.
 - b) Decreased chemotaxis.
 - c) Decreased IL-1 secretion.
 - d) Poor antigen presentation.

The modes of transmission of HIV include:

- 1- Sexual transmission: a) Homosexual or bisexual males (70%) b) Heterosexual partners (4%)
- 2- Intravenous drug abusers (mainly addicts) 18%
- 3- Recipients of blood or blood components, particularly hemophiliacs.
- 4- Organ transplantation from a diseased donor.
- 5- Maternal transmission: a) Transplacental b) Through breast milk.

Pathology: Progressive loss of CD4 cells (which have a high affinity receptor for HIV) → marked immunosuppression. The major pathological features of AIDS include:

- 1- **Opportunistic Infections:** These are very common and include:
 - a) Bacterial infections as tuberculosis, atypical mycobacteriosis, salmonella & shigella infections.
 - b) Fungal infections: as Candidiasis (commonly disseminated) & cryptococcosis (involving CNS).
 - c) Viral infections: as CMV and Herpes simplex virus infections.
- 2- **Protozoal and Helminthic Infections:** as:
 - a) Pneumocystis carinii pneumonia (in 50% of cases) → bilateral lung affection in the form of marked alveolar damage, oedema and inflammation. It may be followed by dissemination.
 - b) Toxoplasmosis → pneumonia or CNS infection.
 - c) Cryptococcosis or isosporidiosis → enteritis.
 - d) Strongyloidosis → pneumonia, CNS infection or disseminated infection.

2- Malignant Neoplasms:

- 1- **Lymphomas (Non-Hodgkin's B cell lymphomas).**
- 2- **Kaposi's Sarcoma:** This is a malignant vascular neoplasm characterized by cutaneous & visceral lesions which grossly appear as purple patches or nodules and microscopically consist of endothelium-lined vascular channels associated with sheets of plump spindle cells, showing slit-like vascular spaces filled with erythrocytes. Kaposi's sarcoma occurs in about 25% of AIDS patients.

3- Generalized lymph node enlargement: There is initial B Cell (follicular) hyperplasia, followed by generalized lymphocyte depletion.

4- CNS Pathology: The CNS is a major target of HIV infection. Neuronal damage, probably by cytokines released from the infected monocytes. Opportunistic infections involving the CNS result in significant nervous damage e.g. meningitis, peripheral neuropathies and progressive encephalopathy (AIDS-dementia complex).

Clinical phases of HIV infection:

- 1- **Initial/early phase:** Nonspecific symptoms as fever, sore throat, muscle pain & skin rash. There is marked viral replication which evokes an immune response.
- 2- **Latent phase:** Asymptomatic phase that lasts for several years. Viral replication is low.
- 3- **Final phase:** Collapse of immunity → opportunistic infections, LN enlargement, tumors, CNS pathology and viral replication.

EPSTEIN BARR VIRUS (EBV) INFECTION

It is transmitted by direct contact and can cause many diseases as:

- 1- **Infectious mononucleosis** characterized by fever, generalized lymphadenopathy, tonsillar enlargement & hepatosplenomegaly.
- 2- Nasopharyngeal carcinoma.
- 3- **Burkitt's lymphoma**.
- 4- Other types of malignancy as **Hodgkin's lymphoma**.

HUMAN PAPILLOMA VIRUS (HPV) INFECTION

There are many types of HPV which can cause many diseases:

1. Benign as skin warts and genital warts.
2. Malignant as squamous cell carcinoma of tongue and female cervix.

CYTOMEGALIC INCLUSION DISEASE (CID)

CID is due to infection with a subtype of herpes virus called **cytomegalovirus (CMV)**. The infected cells show characteristic large intranuclear inclusion bodies. There are 2 main forms of the disease.

- 1- **Congenital transplacental transmission** from the mother. The possible results are:
 - a) Abortion or still birth.
 - b) **Severe multisystem illness:** Jaundice, hepatosplenomegaly, anemia & thrombocytopenia. Other involved systems include salivary glands, kidneys, lungs, pancreas, thyroid & brain. Survivors develop mental retardation.
 - c) **Milder multisystem illness** in the form of intestinal pneumonia, hepatitis and encephalitis. Most of these infants recover, but a few may later be mentally retarded.
 - d) Rarely the infant is totally asymptomatic, but may develop delayed onset mental retardation.

2- Acquired transmission may be through breast milk to infants, or it may affect older persons through respiratory secretions, blood transfusions, organ grafts, fecal-oral transmission or venereal transmission. The clinical possibilities range between totally asymptomatic infections to serious **multisystem illness** (particularly in immunosuppressed transplant recipients and in AIDS). The effects include pulmonary infection sometimes progressing to adult respiratory distress syndrome, intestinal necrosis and ulceration resulting in debilitating diarrhea and chorioretinitis. The central nervous system is usually spared.

MEASLES

Aetiology:

Measles is the most infectious viral disease, transmitted by droplet infection. Incubation period is 1-2 weeks.

Pathology:

- 1- Catarrhal inflammation of respiratory mucosa.
- 2- Generalized skin rash composed of macules and papules.

- 3-Koplik's spots** these are tiny hyperemic spots in the buccal mucosa.
- 4-Lymph node enlargement (cervical)** due to lymphoid hyperplasia and inflammation (which is characterized by numerous giant cells called **Warthin-Finkeldey giant cells**)
- 5-Giant cell pneumonia** may occur.

Complications:

- 1-Encephalitis (rare).
- 2-Secondary bacterial infection may occur in lungs leading to septic bronchopneumonia.

Aetiology: **Rubella virus** Incubation period is 2-3 weeks.

Pathology:

- The disease is mild and self limited characterized by upper respiratory catarrhal inflammation, macular skin rash and generalized lymph node enlargement.
- If it affects pregnant ladies it may lead to congenital fetal anomalies.

VARICELLA-ZOSTER DISEASES

Varicella-zoster (VZ) virus can produce two different diseases (according to age & immunity):

1-Chicken pox (Varicella): A disease of children, transmitted by direct contact and may occur in epidemics. It is usually mild. It is manifested by fever and a skin rash composed of vesicles, most numerous on face and trunk. The vesicles rupture and skin regeneration occurs without scarring. However if secondary bacterial infection occurs, scarring develops. Complications (mainly encephalitis) are very rare & only occur in severe cases.

2-Herpes-zoster (Shingles): This is a severe disease affecting the dorsal root ganglia and is characterized by erythematous vesicular eruption along the course of sensory nerves. The skin of face and trunk is the most commonly affected site. Pain and fever are usual. Serious ocular or cerebral involvement may occur.

Aetiology:

Small pox virus. Incubation period about 2 weeks. This viral disease is almost eradicated from the world.

Pathology:

- 1-Skin rash (macules, papules, vesicles & pustules) Healing results in disfiguring scars.
- 2-Hemorrhagic inflammation of skin, mucous membranes, lungs and other organs as heart (endocarditis) and brain (encephalitis).
- 3-Acute splenic enlargement.

PARASITIC INFECTIONS

VIP

SCHISTOSOMIASIS (BILHARZIASIS)

DEFINITION & AETIOLOGY Bilharziasis is a chronic granulomatous disease caused by Schistosoma infection. The disease is endemic in Egypt and is caused by one of the following two species (sometimes mixed): 1-Schistosoma hematobium: It affects the genitourinary system. 2-Schistosoma mansoni: It affects the digestive system.

LIFE CYCLE: Cercaria penetrate skin → small venules → systemic veins → right side of heart → lungs → left side of heart → systemic circulation through which Schistosoma hematobium reaches vesical, prostatic & utero-vaginal venous plexus, while Schistosoma mansoni reaches mesenteric veins. In these sites worm maturation occurs and deposition of ova starts. Ova of S. hematobium pass to urine and those of S. mansoni pass to stools where they hatch → miracidia → snails → cercaria.

GENERAL PATHOLOGICAL FEATURES:

Bilharzial lesions represent hypersensitivity reactions (types I and IV). The lesions include:

1- LESIONS PRODUCED BY CERCARIA: Acute allergic dermatitis develops at sites of skin penetration by the cercaria.
Grossly: Maculopapular skin rash.
Microscopically: Dilated capillaries, neutrophils, eosinophils and macrophages.

2- LESIONS PRODUCED BY ADULT WORMS: Adult worms live inside veins around bladder (S. hematobium) or colon (S. mansoni).

a) Dead worms → severe venous wall necrosis & inflammation (neutrophils, eosinophils & macrophages) = **thrombophlebitis**

b) Living worms produce:

- Brown bilharzial pigment which is engulfed by phagocytic cells of liver, spleen & other tissues (see parasitic pigmentation).
- Ova.

3- LESIONS PRODUCED BY OVA

a) Recurrent bleeding (due to injury by the spines of ova) leads to anemia. bleeding is in the form of hematuria or blood passing with stools.

b) Some ova may be trapped in the wall of bladder or intestine, or may be carried in blood & become trapped in lungs, liver or rarely other sites. Miracidia of these trapped ova produce "egg antigens" → sensitization of T lymphocytes → release lymphokines → inflammatory lesions which are commonly (but not always) in the form of periovular **granulomas (bilharziomas)** that develop along three successive phases:

- Cellular granuloma:** Ova are surrounded by macrophages (sometimes in the form of epithelioid cells), eosinophils, some neutrophils, lymphocytes and sometimes giant cells (which may engulf ova). Central necrosis may occur, sometimes associated with numerous eosinophils (eosinophilic abscess).
- Fibrocellular granuloma:** These are cellular granulomas surrounded by fibroblasts & capillaries (granulation tissue).
- Fibrous (healed) granuloma:** These are smaller in size and consist of dense collagen. Inflammatory cells progressively disappear.

4-BILHARZIAL ANTIGENS from worms or ova → hyperplasia of lymphoid & reticuloendothelial cells.

VIP + Colon

BILHARZIASIS OF THE URINARY BLADDER (Bilharzial Cystitis)

AETIOLOGY: Infection with *Schistosoma hematobium*.

PATHOLOGICAL LESIONS:

The heaviest deposit of ova occurs in the most vascular parts, mainly the submucosa (and less frequently the muscosa) of the trigone and posterior wall.

Mild & early lesions are grossly nonspecific (hyperemia and petechial hemorrhages). Ova are detected microscopically.

Severe & prolonged cases develop specific lesions which include:

1- **Sandy Patches:** These are very common bladder lesions.

Pathogenesis: Large numbers of ova trapped in the submucosa, associated with dystrophic calcification → pressure atrophy of the overlying mucosa.

Gross: Irregular grayish gritty patches covered by thin atrophic mucosa.

Microscopy: The submucosa shows a large number of calcified ova surrounded by dense fibrosis. The mucosa is atrophic.

2- **Bilharzial Polyps:** Less common than sandy patches.

Pathogenesis: A small number of ova is trapped in the submucosa surrounded by inflammation. Repetition of the process leads to mucosal elevation associated with mucosal hyperplasia and polyp formation.

Gross: Single or multiple polyps which may be sessile, pedunculated or complex branching polyps. The polyps are reddish and show granular cut surface. They are 2-20 mm or more in diameter.

Microscopy: Polyp consists of:

- A core of connective tissue derived from the submucosa showing ova surrounded by macrophages, lymphocytes, eosinophils & fibroblasts.
- A covering hyperplastic mucosa.

3- **Bilharzial Ulcers:** These are common bladder lesions (20%).

Pathogenesis:

- Mucosal damage by large number of ova penetrating the mucosa associated with inflammation, necrosis and mucosal shedding.
- Shedding of the atrophic mucosa of sandy patches.
- Ulceration of a polyp.

Gross:

- Single or multiple ulcers; small or large, but usually less than 1 cm in diameter.
- Edges are sharp, floor is granular (due to ova) and may show calcification. Base is firm (fibrosis).
- May be superficial (shallow or saucer ulcers), deep (excavating ulcer) or very deep due to retraction of dense fibrosis (fissure ulcer).

Microscopy: Edges, floor and base of ulcers show ova surrounded by inflammatory cells and fibrosis.

4- **Dense Fibrosis:** In long standing severe cases, fibrosis may be extensive.

5- **Epithelial (Urothelial) Changes** (very common): The transitional mucosa has a great capability to undergo hyperplastic, metaplastic & dysplastic changes in response to chronic irritation. May be precancerous.

* a) **Hyperplasia.**

* b) **Brunn's nests:** These are solid buds of transitional cells present in the submucosa due to focal dipping of the hyperplastic urothelium.

* c) **Cystitis cystica:** These are cysts lined by transitional epithelium. They are believed to be due to central degenerative changes in Brunn's nests. They are usually of microscopic size, but may enlarge and become grossly visible as pale mucosal vesicles, few millimeter in diameter.

* d) **Cystitis Glandularis:** These are cysts lined by mucin-secreting columnar cells (similar to colonic epithelium). The origin is unclear, probably metaplasia of cystitis cystica. The lesion is precancerous.

* e) **Squamous metaplasia & Leukoplakia:** Squamous metaplasia is very common. It may be associated with extensive keratinization & appear as thick white patches (leukoplakia). These lesions are precancerous.

* f) **Dysplasia & carcinoma in situ.** These lesions are precancerous.

Remark: No similar epithelial changes occur in intestinal bilharziasis.

COMPLICATIONS OF BILHARZIAL CYSTITIS:

1- Recurrent hematuria leads to anemia.

2- Secondary bacterial infection. This may lead to:

- Calcium phosphate stone. Alkaline change of pH of urine (due to infection) → calcium phosphate deposition.
- Fistulae with rectum or vagina.

3- Bladder neck obstruction due to fibrosis. This leads to:

- Hypertrophy and dilatation of the bladder.
- Bilateral hydronephrosis and bilateral hydroureter. ★★
- Chronic renal failure due to bilateral hydronephrosis. ★★

4- Bladder carcinoma ★★★★★

5- Spread of bilharziasis mainly leads to pulmonary bilharziasis. ★

BILHARZIASIS OF OTHER PARTS OF THE UROGENITAL SYSTEM

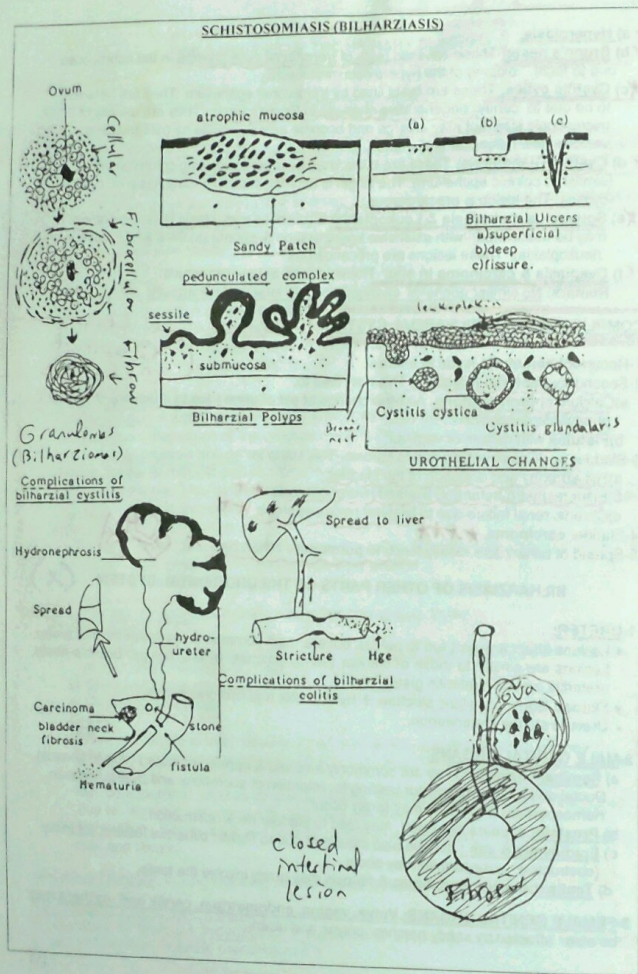
1- URETER:

- Lesions affect any part (up to pelvis), but are most common in the lower third of ureter. Lesions are similar to those of bladder (sandy patches, ulcers, polyps, Brunn's nests, ureteritis cystica, ureteritis glandularis...).
- Fibrosis leads to ureteric stricture → hydronephrosis and hydroureter.
- Ureteric stones are common.

2- MALE GENITAL ORGANS:

- Seminal vesicles:** They are commonly involved & appear indurated (due to fibrosis). Ductal obstruction may occur leading to retention of secretions and cystic dilatation. Hemospermia & infertility may rarely occur.
- Prostate:** appears indurated, may lead to bladder neck obstruction.
- Epididymis & vas:** may be also indurated due to fibrotic bilharzial lesions. Infertility (obstructive azospermia) may occur.
- Testis:** bilharzial granulomas & fibrosis may rarely involve the testis.

3- **FEMALE GENITAL ORGANS:** Vulva, vagina, endometrium, cervix and urethra may be also affected by sandy patches, polyps and ulcers.



* No Carcinoma in Large Intestine

BILHARZIASIS OF LARGE INTESTINE (Bilharzial Colitis)



Define

AETIOLOGY: Infection with *Schistosoma mansoni*

PATHOLOGICAL LESIONS:

Bilharziasis of the gastrointestinal tract is commonest in the colon particularly the rectum. The heaviest deposit of ova occurs in the submucosa. In severe cases ova are seen in musculosa and sometimes the serosa. The small intestine is less commonly affected. Gastric involvement is very rare.

MILD & EARLY LESIONS

Mucosal hyperemia & petechial hemorrhages. Ova are microscopically seen.

SEVERE & PROLONGED CASES develop specific lesions:

1. **Bilharzial Polyps:** These are the most common intestinal lesions.

Pathogenesis: Repeatedly trapped small numbers of ova in the submucosa → gradually increasing inflammation → mucosal elevation associated with mucosal hyperplasia → polyp

Gross: Single or multiple polyps which may be sessile, pedunculated or complex branching. The polyps are reddish and measure 2-20 mm or more in diameter.

Microscopy: Polyp consists of a core of connective tissue showing ova surrounded by macrophages, lymphocytes, eosinophils & fibroblasts. The covering mucosa is hyperplastic.

Secondary changes:

- Ulceration
- Secondary infection of ulcerated polyps → bilharzial dysentery
- Fibrosis

2. **Sandy Patches:** Rare.

3. **Bilharzial Ulcers:**

Pathogenesis: Bilharzial ulcers may be due to:

- Mucosal damage caused by penetrating ova.
- Avulsion of polyps
- Detachment of atrophic mucosa of sandy patches.

Pathology: Ulcers are irregular, small or large, usually superficial with granular floors and firm bases. Microscopy shows ova surrounded by inflammatory cells and fibrosis.

4. **Fibrosis:** Variable degrees of fibrosis occur. It may be extensive in severe long standing cases affecting all bowel layers → compression of venous radicles within the intestinal wall → worms deposit ova outside the intestinal wall → indurated peritoneal nodules or a bilharzial pericolic mass. In these patients ova may not be detected in their stools (closed intestinal bilharziasis).

COMPLICATIONS:

1. Recurrent intestinal hemorrhages → anemia.
2. Secondary infection (mainly after polyp ulceration) → dysentery (bilharzial dysentery).
3. Intestinal obstruction is uncommon. It may develop due to a) fibrous Stenosis, b) large polyps may rarely cause lumen obstruction c) Intussusception due to abnormal peristalsis.
4. Spread → bilharziasis of liver and sometimes lungs.
5. Intestinal bilharziasis does not lead to carcinoma.

BILHARZIASIS OF LIVER (Bilharzial Hepatic Fibrosis)

PATHOGENESIS & MICROSCOPY:

1-The **Portal Tracts** show major changes:

- Ova** (carried as emboli through the portal vein) → portal tracts → granulomas → fibrosis
- Dead Worms** may be trapped inside venules of the coarse tracts → thrombophlebitis
- Angiomatoids**: These are dilated capillaries seen in the fibrotic tracts. They represent dilated collateral channels between branches of the hepatic artery & portal veins.

2-The **Hepatic Lobules** show minimal insignificant lesions:

- Framework (architecture)** is preserved. Therefore cirrhosis does not develop unless another lesion is superimposed (as hepatitis B or C).
- Kupffer Cells** engulf brown pigment excreted from living worms.
- Hepatocytes** may show minimal steatosis, probably due to anemia.

GROSS FEATURES:

- Early the liver is enlarged. Later with progressive portal fibrosis the liver becomes shrunken, firm, with irregular surface and thickened capsule.
- Cut section may show dark brown coloration (bilharzial pigment). The fibrotic fine portal tracts appear as delicate grayish bands & the fibrotic coarse tracts appear as thick grayish collars around branches of the portal vein → appearance resembling patent pipes (pipe stem fibrosis).

EFFECTS AND COMPLICATIONS:

1-Portal Hypertension:

Pathogenesis:

- Portal fibrosis leads to compression of portal veins.
- Angiomatoids convey the high pressure of the hepatic artery to the portal veins.

Effects:

- Splenomegaly.
- Ascites.
- Opening of porto-systemic venous collaterals. This leads to:
 - Oesophageal varices which may rupture → hematemesis.
 - Piles → bleeding per rectum.
 - Caput medusae.

2-**Portal Vein Thrombosis**: may occur due to vascular stasis.

3-**Mild disturbances of liver functions & lowering of plasma proteins**

4-**Ascites** due to portal hypertension and lowering of plasma proteins.

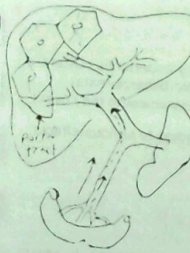
5-**Ammonia encephalopathy**: It may complicate hepatic Bilharziasis, particularly those cases having superimposed active hepatitis C or B infection. The mechanism is explained as follows:

- Normally ammonia produced by bacterial action within the colon is converted in the liver to urea. Therefore under normal conditions ammonia does not reach the systemic circulation.
- In cases of hepatic portal fibrosis complicated by active hepatitis:
 - The diseased liver cells may not adequately convert ammonia into urea.
 - The open porto-systemic collaterals (due to portal hypertension) allow ammonia to reach the systemic circulation → brain → encephalopathy (which may end in coma).

CAUSES OF DEATH IN HEPATIC BILHARZIASIS:

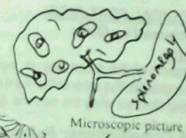
- Bleeding (hematemesis)
- Superimposed chronic viral hepatitis → cirrhosis & liver failure

portal tract involvement
by ova or worms coming
from intestine

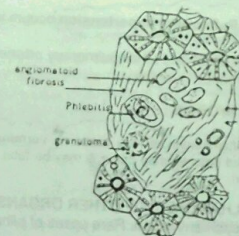


HEPATIC BILHARZIASIS

Gross picture of liver
(shrunken with irregular surface
& thick portal tracts)



Microscopic picture



Pigmented Kupffer cells

HCG

BILHARZIAL SPLENOMEGALY

Pathogenesis & Pathology:

1-Early Enlargement

Pathogenesis: Lymphoid & reticuloendothelial hyperplasia in response to bilharzial antigens

Gross Features: Mild enlargement, up to 300 g (normal = 150 g).

Microscopic Features: Lymphoid hyperplasia.

2-Late Enlargement

Pathogenesis: Portal hypertension (due to hepatic bilharzial fibrosis) → progressive sinusoidal congestion.

Gross Features: Marked enlargement, up to 1-3 kg or more. Cut section is darkly congested.

Microscopic Features:

- Marked congestion of the sinusoids. Pressure atrophy of the follicles may occur.
- Phagocytic cells (littoral cells) contain brown pigments (bilharzial pigment & hemosiderin).
- Rupture of congested sinusoids → hemorrhage → hemosiderin → fibrosis → **fibrosiderotic nodules** (Gumma Gandy nodules). These nodules show positive Prussian blue reaction.

Effects And Complications:

- Compression of adjacent structures as stomach or diaphragm.
- Hypersplenism → pancytopenia (anemia, leucopenia and thrombocytopenia).

BILHARZIASIS OF LUNGS

PATHOGENESIS:

Lung bilharziasis develops in up to 20% of bilharzial patients, *S. hematobium* is more common than *S. mansoni*. Ova & rarely dead worms reach the lungs through one of the following routes:

- 1-S. hematobium: From vesical veins → iliac veins → inferior vena cava → lungs.
- 2-S. hematobium: From vesical veins → vertebral veins → pulmonary vessels
- 3-S. mansoni: Through porto-systemic collaterals, which develop in cases of hepatic bilharziasis.

PATHOLOGICAL FEATURES:

1-Lesion caused by OVA:

Pathology:

- a) Penetration of the arterioles → necrotizing arteriolitis followed by endarteritis obliterans
- b) Ova trapped in the interstitial tissue of the lungs → granulomata (bilharziomata).
- c) Interstitial fibrosis may be severe & dilated vascular channels (angiomatoids) may occur.

Effects & Complications: Pulmonary hypertension occurs leading to serious effects:

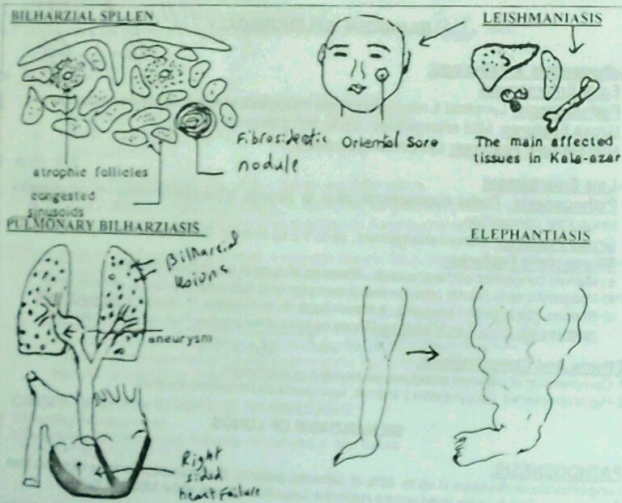
- a) Right-sided heart failure.
- b) Atherosclerosis of medium-sized and small pulmonary arteries.
- c) Aneurysm of the main pulmonary arteries

2-Lesions caused by DEAD WORMS:

- a) Necrosis of vascular walls.
- b) Necrosis & severe allergic inflammation of lung tissue → verminous pneumonia. In severe cases confluence of consolidated patches may occur & may be fatal. Surviving patients develop fibrosis & dystrophic calcification.

BILHARZIASIS OF OTHER ORGANS

Emboli of bilharzia ova can reach any organ. Rare cases of bilharzial reaction of the spinal cord, brain, lymph nodes, and other sites were recorded.



LEISHMANIASIS

A protozoal disease transmitted to man by the bites of sand fly. Two main types:

1-CUTANEOUS LEISHMANIASIS (Oriental Sore):

Definition & Aetiology: Cutaneous ulcers caused by Leishmania tropica organisms.

Gross: Exposed parts as face and limbs develop a papule at the site of bite of the sand fly. The papule then ulcerates followed by healing with dense scar.

Microscopy: A chronic inflammatory reaction with numerous macrophages engulfing the organisms. The vascular endothelium may also be invaded by the organisms

2-VISCERAL LEISHMANIASIS (Kala-azar):

Definition & Aetiology: Infection with Leishmania donovani organisms, which selectively affect the reticuloendothelial cells of the viscera.

Pathology: The organisms settle inside macrophages of different organs. This leads to hepatosplenomegaly, lymph nodes enlargement and anemia and leucopenia due to bone marrow affection. The immunity is lowered and death may occur due to superimposed infections as pneumonia.

FILARIASIS

(Bancroftian Filariasis)

AETIOLOGY:

The disease is transmitted by the bites of the Culex pipiens mosquitoes, which inoculate microfilaria of the Wuchereria bancrofti in the skin. These microfilaria migrate to lymphatics and lymph nodes (most commonly those of lower limbs and external genitalia) where they mature into adult worms.

PATHOLOGY:

1-Lymphangitis and Lymphadenitis: Inguinal, femoral and popliteal nodes are the most commonly affected nodes. Inflammation is mainly caused by dead worms and includes types I and IV hypersensitivity reactions. Necrosis and liquefaction may occur (filarial abscess). Fibrosis will ultimately cause lymphatic obstruction → dilatation of lymphatics (lymphatic varix)

2-Lymphatic Obstruction:

Mechanism:

1-Mechanical obstruction of the lymphatic lumen by worms.

2-Filarial lymphangitis

3-Secondary streptococcal infection (streptococcal lymphangitis) → fibrosis & obstruction.

Effects:

1-Elephantiasis: It develops in 10-15 years. It mainly affects the lower limbs. The affected limb is progressively enlarged and the skin appears markedly thickened, rough & fissured. This is due to progressive lymphoedema associated with progressive fibrosis. Similar changes can occur in scrotum and vulva.

2-Chylous (lymph) Effusions including chylous ascites, chylothorax, chylocele. These are due to rupture of lymphatic varix...

3-Filarial Funiculitis: This is affection of the spermatic cord with filarial granulomata, filarial abscesses and fibrosis. The condition is not uncommon.

MALARIA

Definition & Aetiology:

This is a protozoal disease caused by Plasmodium (4 species) and transmitted by mosquitoes.

Pathological Features:

- Anemia (due to hemolysis of red blood cells in which the parasite lives).
- Production of malarial pigment which is engulfed by reticuloendothelial cells causing their hyperplasia observed in the bone marrow, liver (leading to hepatomegaly) and spleen (leading to splenomegaly).
- In cases of Plasmodium falciparum species, malignant pernicious malaria may occur characterized by sludging of parasitized red cells within the visceral capillaries (visceral tide) with absence of parasites from erythrocytes of the peripheral capillaries. Visceral red cell sludging → decreased peripheral circulation → severe anoxia and serious effects.

HYDATID DISEASE

Aetiology:

Eggs of the tapeworm "Echinococcus granulosus" pass in the stools of infected dogs & are occasionally ingested by man. The released larvae reach the liver & sometimes other organs where they form hydatid cysts.

Pathological Features: One or more hydatid cysts develop. Common sites are liver, spleen & lungs. Brain and other organs may be affected. The cyst may reach up to 20 cm in diameter. It may be surrounded by chronic inflammatory cells, eosinophils and fibrosis. Structurally hydatid cysts consist of an outer laminated elastic layer & an inner germinal layer showing broad capsules containing scolices. Cyst lumen contains hydatid fluid.

Complication of hydatid cysts:

- 1-Pressure effects on surrounding tissue
- 2-Secondary infection leading to abscess & toxemia
- 3-Rupture leading to: a) Allergic manifestations up to anaphylaxis b) secondary hydatid cysts.

ANKYLOSTOMIOSIS

Definition & Aetiology:

Helminthic disease caused by penetration of the skin with ankylostoma larvae.

Pathological Features:

- Larvae in the ground penetrate the skin of feet causing dermatitis (ground itch).
- Larvae circulate and reach the lungs causing transient bronchopneumonia.
- Adult stage: The parasites live in small intestine particularly duodenum and 1st portion of jejunum causing mucosal damages and hemorrhages. This leads to microcytic anemia which may be severe enough to cause parenchymal degenerations as liver & heart steatosis

TOXOPLASMOSIS

AETIOLOGY: Toxoplasmosis is a common protozoal infection caused by Toxoplasma gondii. Man is infected by ingesting oocysts deposited in the soil (from infected animals as cats) or by eating insufficiently cooked meat of chronically infected animals.

PATHOLOGY:

- 1-Lymph node enlargement, most commonly the posterior cervical nodes. Other cervical nodes & generalized lymph node enlargement may sometimes occur. The microscopic features of toxoplasma lymphadenitis include hyperplasia of lymphoid follicles & epithelioid cell aggregates without giant cells. The organisms may be demonstrated by the Giemsa stain inside macrophages
- 2-Transplacental transmission → abortion or severe foetal lesions
- 3-Disseminated toxoplasmosis in immunocompromised persons as in AIDS. It is almost fatal as a result of pneumonia, myocarditis or encephalitis.

NUTRITIONAL DISORDERS (MALNUTRITION)

CHAPTER XIV

Malnutrition is suboptimal nutrition; either in excess or deficiencies. Thus it includes

- 1- Obesity
- 2- Undernutrition.

OBESITY:

Aetiological factors:

Obesity is overweight relative to dietary over-intake & may have genetic predisposition. It is aggravated by defective physical exercise. Some endocrine disorders (& drug medication) cause obesity (as Cushing's syndrome)

Diseases caused by obesity:

- 1-Diabetes mellitus
- 2-Hypertension
- 3-Atherosclerosis
- 4-Higher incidence of thrombosis (due to hyperlipaemia, atherosclerosis & other factors)
- 5-Heart disease
- 6-Increased risk of developing cancer (particularly of GIT)

UNDERNUTRITION:

Types of undernutrition:

- 1-Total (starvation)
- 2-Selective as:
 - vitamin deficiency
 - protein deficiency (protein calorie undernutrition)

The causes of undernutrition:

- Decreased diet intake as in cases of Dysphagia and anorexia nervosa
- Malabsorption states
- Increased requirements as in infants & children due to their rapid rate of growth
- Malignant cachexia (see chapter VI)
- Other factors including genetic disorders

PROTEIN CALORY UNDERNUTRITION:

It is also called protein energy malnutrition (PEM). It is most common in poor countries (third world). It is most serious if it affects growing infants resulting in either:

- 1) **Kwashiorkor:** characterized by apathy, generalized oedema, increase of subcutaneous fat, moon face and fatty liver (hepatomegaly) with low serum albumin.
- 2) **Marasmus** characterized by severe wasting including subcutaneous fat associated with stunted growth and premature aging features. In contrast to Kwashiorkor, these infants are alert (non-apathetic) and hungry with no oedema or hepatic enlargement

VITAMIN DEFICIENCIES

VITAMIN D DEFICIENCY

2011 10/11 X 1) RICKETS

DEFINITION:

Rickets is a disease of infants characterized by defective bone mineralization (calcium & phosphate) resulting in bone softening and abnormalities of bone growth

AETIOLOGY:

- 1-Vitamin D deficiency; commonly due to lack of exposure to sun.
- 2-Chronic renal disease (renal rickets).
- 3-Deficiency of calcium & phosphorus
- 4-Hereditary (X-linked dominant) vitamin D resistant rickets. Rare.

PATHOGENESIS:

- 1-The disease affects infants during the first two years of age. Premature infants are more susceptible because they already have inadequate calcium. The resulting deformities remain for life.
- 2-Normally bone growth occurs by proliferation of cartilage cells at the epiphyseal line followed by calcification of the cartilage matrix, which leads to degeneration of cartilage, then invasion of this area by osteoblasts and capillaries with deposition of soft matrix (this soft bone is called osteoid tissue). Further calcification of osteoid tissue changes it into hard osseous tissue.
- 3-In rickets failure of calcification leads to
 - a) Cartilage hypertrophy leading to various effects as rachitic metaphysis (thick epiphyseal cartilage plate) and hypertrophy of costochondral cartilage
 - b) Osteoid will form but without changing into osseous tissue.

PATHOLOGY:

1-Skeletal Lesions:

- **Skull**
 - a) Delayed closure of fontanelles.
 - b) Delayed eruption of teeth.
 - c) Craniotabes (flattening of occipital bones, due to their softening)...
 - d) Bossing of frontal and parietal bones.
- **Vertebrae:**
 - a) **Dorsal kyphosis:** Backward bending.
 - b) **Lumbar lordosis:** Forward bending.
 - c) **Scoliosis:** Lateral bending.
- **Chest:**
 - a) **Rosary Chest:** Beaded costo-chondral junctions due to masses of osteoid that develop at the costo- chondral junctions
 - b) **Harrison's sulcus:** A groove opposite insertion of diaphragm (transverse line across the lower rib
 - c) **Pigeon Chest:** Flattening of chest sides and forward protrusion of the sternum.
- **Long bones:**
 - a) Bowing of weight-bearing bones and pathological fractures.
 - b) **Rachitic metaphysis:** Thick epiphyseal cartilage plate due to growth of cartilage without significant cartilage degeneration caused by defective calcification.
- **Pelvis:** Narrowed contracted trifol pelvis

2-Somatic Lesions:

- **Lymphoid hyperplasia of lymph nodes and spleen.**
- **Weak muscles & weak joint ligaments**

3-General Effects:

- Muscle weakness leads to protrusion of abdomen (pot belly).
- Limited movement may lead to overweight
- Delayed sitting, standing and walking.

COMPLICATIONS OF RICKETS:

- 1-Bone deformities
- 2-Pathological fracture
- 3-Infections due to low immunity.
- 4-Future labour problems in female patients (narrow pelvis).

II) OSTEOMALACA

It is the adult counterpart of infantile rickets. It mainly affects adult females due to deficiency of calcium & vitamin D as a result of repeated pregnancies and lactations. Bone turnover is disturbed, where the normal bone resorption is replaced by osteoid tissue (poorly calcified bone). Bone becomes porous & soft resulting in: 1) Bowing of legs & pathological fracture 2) Trifol pelvis 3) Lumbar lordosis.

VITAMIN A DEFICIENCY

Vitamin A deficiency results in:

1-Skin & mucous membranes:

- a) Hyperkeratosis of skin (appears dry & scaly)
- b) Squamous metaplasia

2-Eye:

- a) Night blindness
- b) Xerophthalmia (dry eyes due to keratinization of lacrimal glands).
- c) Keratomalacia (softening of the cornea)

3-Retarded growth in children

VITAMIN K DEFICIENCY

Aetiology:

- 1-Prolonged use of broad spectrum antibiotics (due to killing of intestinal bacteria that synthesize vitamin K
 - 2-Obstructive jaundice (since vitamin K is a fat soluble vitamin needing bile for its digestion & absorption)
 - 3-Temporary deficiency in newly born infants.
- Pathological effects:** Vitamin K deficiency → defective formation of prothrombin →
- 1-Hemorrhagic tendency e.g. interstitial hemorrhage due to minimal trauma.
 - 2-Prolonged bleeding e.g. prolonged post operative hemorrhage

VITAMIN C DEFICIENCY: SCURVY

Vitamin C deficiency is rare. It leads to defective formation of ground substance and collagen resulting in:

- 1-**Bone** : Poor transformation of calcified cartilage into bone due to defective formation of osteoid will result in bone weakening, fractures and defective bone healing.
- 2-**Teeth**: Defective formation of teeth in children associated with teeth loosening
- 3-**Wound healing** : Defective wound healing due to poor formation of collagen.
- 4-**Hemorrhage**: Due to poor formation of cement in the capillary walls, hemorrhages are common which may be mild (petechial) , mostly in the gums , but may be severe hemorrhage from nose, GIT or subcutaneous tissue. Repeated hemorrhages lead to anemia..

VITAMIN B DEFICIENCY

I)PELLAGRA

Definition : Pellagra (which means rough skin) is a disease caused mainly by nicotinic acid deficiency

Aetiology: Nicotinic acid deficiency mainly occurs in people who depend on maize as the main source of starch, since maize is deficient in tryptophane from which nicotinic acid is synthesized.

Pathology:

1-Skin (Dermatitis) : The parts exposed to sun show hyperemia, vesicles then become scaly. Microscopically there is hyperkeratosis of the epidermis associated with dermal inflammation.

2-GIT lesions: Painful inflamed tongue and Diarrhea due to colonic inflammation

3-CNS:

a)Demyelination of lateral and posterior columns (subacute combined degeneration).

b)Degeneration of nerve cells→ dementia

II) BERI BERI

Definition & Aetiology: A disease caused by deficiency of vitamin B1.

Pathology:

1-**Dry beri-beri**: Peripheral neuritis affect the cranial and spinal sensory and motor nerves due to degeneration of myelin and axis cylinders.

2-**Wet beri-beri**: The heart, mainly the right side is affected and shows fatty change and dilatation. Congestive heart failure may occur leading to generalized oedema (& hence the name wet beri-beri)

III)VITAMIN B12 AND/OR FOLIC ACID DEFICIENCY

See macrocytic anemia in systemic pathology.

CHAPTER XV

GENETIC DISORDERS

TYPES OF MUTATIONS

Genetic disorders occur due to mutations .Mutation is defined as permanent damage of DNA. Mutations that affect the germ cells are transmitted to the progeny and may give rise to inherited diseases. Mutations affecting somatic cells do not cause inherited (hereditary) disease ,but are important factors in the development of cancer and some congenital malformations. Mutations are classified into three categories:

- 1-**Genome mutations**: These involve loss or gain of a whole chromosome ,giving rise to monosomy or trisomy. Thus genome mutations affect the number of chromosomes.
- 2-**Chromosome mutations**: Structural changes within a chromosome due to re-arrangement of genetic material.
- 3-**Gene mutations** affecting individual genes within a chromosome.

CLASSIFICATION OF GENETIC DISORDERS

- 1-Mendelian disorders.
- 2-Disorders of multifactorial inheritance.
- 3-Single gene disorders with non-classic inheritance.
- 4-Cytogenetic (chromosomal) disorders.

I) MENDELIAN DISORDERS

They are caused by mutations affecting single genes. More than 4500 disorder were listed. These disorders are inherited either as autosomal dominant, autosomal recessive or X-linked inheritance. It has to be remembered that each gene is represented as a pair (alleles) on a specific gene locus on the corresponding chromosomes.

A) AUTOSOMAL DOMINANT DISORDERS:

Definition:These are disorders manifested in the heterozygous state i.e. resulting from mutation affecting one of a paired allele; the other not necessarily affected. Mutations of autosomal dominant disorders affect key structural proteins as collagen of connective tissue and spectrin of erythrocytes and also affect proteins that regulate metabolic pathways such as membrane receptors and transport proteins.

Examples of autosomal dominant diseases: 1) Nervous disorders such as neurofibromatosis 2)Renal disorders such as adult type of polycystic kidney 3)Gastrointestinal disorders as familial polyposis 4) Skeletal disorders such as Marfan syndrome 5)Haemopoietic disorders such as hereditary spherocytosis 6)Metabolic disorders such as familial hypercholesterolaemia 7)Bone disorders such as multiple exostosis

B) AUTOSOMAL RECESSIVE DISORDERS:

Definition:These are disorders manifested in the homozygous state i.e. resulting from mutation affecting both of a paired allele. Abnormality of one allele without its corresponding allele results in a heterozygous carrier state without clinical manifestations.

Examples of autosomal recessive diseases: 1) Nervous disorders such as spinal muscular atrophy 2)Renal disorders such as infantile type of polycystic kidney 3) Haemopoietic disorders such as sickle cell anemia and thalassemias 4)Metabolic disorders such as cystic fibrosis, phenylketonuria, galactosemia, α_1 antitrypsin deficiency, haemochromatosis, Wilson's disease & hemochromatosis

C) X-LINKED DISORDERS:

Definition: Disorders resulting from a mutant gene existing in the X chromosome

Types: May be recessive or rarely dominant:

1-X-linked recessive disorders: The abnormal (mutant) gene is of a recessive nature. Thus females are carriers and do not suffer from a clinical disease since the other allele is normal, while males suffer from a disease since the abnormal gene has no corresponding allele on the Y chromosome.

Examples of X-linked recessive disorders include 1) Skeletal disorders as Duchenne muscular dystrophy 2) Haemopoietic disorders as hemophilia A & B 3) Ocular disorders as colour blindness 4) Immune disorders as agammaglobulinemia 5) Metabolic disorders as diabetes insipidus

2-X-linked dominant disorders (rare). The mutant gene is of a dominant nature, i.e. only one abnormal gene of the alleled pair is sufficient to cause disease; therefore the disease affects both males and females.

Example: vitamin D resistant rickets.

II) CYTOGENETIC (CHROMOSOMAL) DISORDERS

The normal human karyotype of somatic cells is 46 chromosomes including 44 (22 pairs) of autosomes and two sex chromosomes either xy (male) or xx (female). The normal human karyotype (44xy or 44xx) is symbolized as 2n-diploid. The normal gamete (sperm or ovum) karyotype is symbolized as 1n - haploid (22x or 22y)

Chromosomal Abnormalities include:

1-Structural abnormalities:

a-Deletion: This is loss of a chromosome portion. The lost segment may be terminal (through one chromosomal break near its end) or interstitial (due to two breaks).

How to refer to deletion? : State the karyotype, then the number of the affected chromosome then refer to

whether deletion has affected the short arm (p) or long arm (q) of the chromosome then put the signal -

(minus) to denote deletion. Example: 46xy16p- means normal male karyotype with deleted segment of the

short arm (p) of chromosome number 16.

b)Translocation: This is transfer of a deleted segment of one chromosome to another. It may be reciprocal translocation i.e. deletion affects two chromosomes with exchange of deleted segments.

c-Ring chromosome: It is a special form of deletion occurring when deletion occurs at both ends of a chromosome followed by fusion of the damaged ends.

d-Inversion: Two interstitial breaks with inversion (180 degree rotation) of the separated segment within the affected chromosome.

e-Isochromosome: Occurs when one chromosome arm (short or long arm) is lost followed by duplication of the remaining arm, so that the chromosome becomes formed of either two long arms or two short arms.

EXAMPLES OF STRUCTURAL CHROMOSOME ABNORMALITIES:

a-Cri du chat syndrome: The disorder is due to deletion of the short arm of chromosome 5 (5p-). The infant is develops mental retardation, microcephaly, round facies and a characteristic cry of a cat (during infancy).

b-Philadelphia chromosome which results from balanced reciprocal translocation between chromosomes 22 & 9. This cytogenetic disorder is seen in more than 95% of cases of chronic myeloid leukemia.

2-Numerical (number) abnormalities:

a-Euploidy refers to an exact multiple of the normal haploid (23) which may be 2n (normal diploidy or 46), 3n or triploidy (i.e. 69 chromosomes), 4n triploidy ...etc. Abnormal euploidy (3n, 4n...etc.) may be systemic (affecting all cells), this is incompatible with life (fetus is aborted). It may affect some cells (e.g. cancer cells).

b-Aneuploidy refers to abnormalities of chromosome numbers which is not an exact multiple of haploid. Aneuploidy results from non-disjunction of one chromosome during gametogenesis (during meiosis) resulting in one gamete with an extra-chromosome (n + 1) and another gamete with a missing chromosome (n - 1), thus the fertilized ovum (zygote) will be either :

- i) 2n + 1 (47 chromosomes or **trisomy**) or
- ii) 2n - 1 (45 chromosomes or **monosomy**)

c-Mosaicism: It is due to mitotic errors in early development resulting in two or more population of cells in the same individual e.g. 45x/47xxx mosaic or 45x/46xx/47xxx mosaic.

EXAMPLES OF SYNDROMES WITH CHROMOSOME NUMBER ABNORMALITIES:

a- Abnormal number of sex chromosomes:

i) **Klinefelter's syndrome:** Male with a karyotype 47xxy, characterized by atrophic testis, infertility & gynecomastia.

ii) **Turner's syndrome** : Female with karyotype 45x, characterized by atrophic ovaries, infantile external genitalia, underdeveloped breasts, amenorrhea, infertility, normal or subnormal mentality & may be congenital heart disease

iii) **Multi X female** (ranging between 47xxx & 49xxxxx): The affected female is physically normal & fertile, but some show menstrual irregularities and some may have mental retardation (proportionate to the number of X chromosomes)

iv) **47 xyy syndrome:** A normally developed male, tall, with high incidence of criminal behavior.

b- Abnormal numbers of autosomes e.g.:

i) Trisomy 21 (Down syndrome): It is the most common chromosomal disorder and a major cause of mental retardation.

ii) Other trisomies as trisomy 18 (Edwards syndrome) & trisomy 13 (Patau syndrome)

III) MULTIFACTORIAL DISORDERS

These are diseases resulting from genetic as well as environmental disorders e.g

1-**Diabetes mellitus** (genetic error + other factors such as viral infection of pancreas, obesity, stress ... etc)

2-**Hypertension** (genetic factor + other factors as stress, obesity, excess salt in diet ... etc)

CHAPTER XVI

ENVIRONMENTAL PATHOLOGY

Diseases that result from environmental factors include:

I) PHYSICAL INJURY

1-Radiation injury: See chapter VII

2-Temperature injury:

a)Heat (sun) stroke: Exposure to high climate temperature→ over-sweating & vasodilatation→ loss of sodium & water , hypotension, hyperkalemia , dehydration & hypoxia.

b)Frostbite: Exposure to severe cold → vasoconstriction & capillary thrombi→ gangrene of fingers, toes, nose & ears.

3-Electric Injury: The effects vary according to severity of electric current, including skin burns, bone fractures, rupture of organs & vessels , sudden death due to nervous, cardiac or respiratory derangements

4-Physical carcinogens (mainly causing skin cancer) : see chapter VI.

II) CHEMICAL INJURY

1-Carbon monoxide: Combines with hemoglobin (carboxyhemoglobin) which loses its capacity to bind oxygen→ death (with the skin appearing cherry red in color)

2-Insecticides: →CNS disturbances, arrhythmias, impotence & infertility

3-Lead poisoning (plumbism): .Lead may be derived from car exhaust & some paints .It leads to gum pigmentation, chronic interstitial nephritis, neurological symptoms & anemia

4-Methyl alcohol: The type of alcohol in liquors الخمر is ethyl alcohol. An alcoholic person may drink methyl alcohol instead of ethyl alcohol (being much cheaper). The metabolites of ethyl alcohol (formic acid and formaldehyde) are toxic to retina and brain .

4-Chemical carcinogens: see chapter VI.

III) AIR POLLUTION

Sources of air pollution are numerous such as gases, fumes, fibers, dust, bacteria... etc. Air pollution can cause many adverse effects such as:

1-Inflammations as conjunctivitis, bronchitis, dermatitis

2-Immunological disorders and allergy such as bronchial asthma, allergic rhinitis and hay fever

3-Pneumoconiosis (chronic granulomatous lung disease due to inhalation of particles e.g silicosis, asbestosis, byssinosis, bagassosis ... etc).

4-Carcinogens → malignancy (see carcinogens chapter VI)

III) POOR CULTURAL FACTORS

1-Smoking: It predisposes to many diseases such as

a)Atherosclerosis→ coronary heart disease & others.

b)Buerger's disease (thromboangitis obliterans)

c)Chronic obstructive lung disease: chronic bronchitis & emphysema

d)Cancer e.g. bronchogenic carcinoma, oral cancer.. etc.

e)Maternal smoking → fetal hypoxia

2-Alcohol abuse: It predisposes to many conditions as

a)Steatosis (fatty liver)→ alcoholic steatohepatitis (ASH) → cirrhosis

b)Gastritis & pancreatitis

c)Peripheral neuritis

d) Testicular atrophy

e)cardiomyopathy

f)cancer (oropharyngeal & hepatic)

3-Addictive drugs (street drugs, dope) e.g:

a)Bango→ disturbed psychology & adverse behavior, disturbed pulmonary & immunological symptoms

b)Cocaine: It increases dopamine & norepinephrine leading to euphoria, arrhythmias & mental changes.

c)Heroin: It leads to behavioral changes, organ damage (respiratory, cardiovascular... etc), angitis, peripheral neuritis & transmitted infections (through contaminated syringes) as AIDS, infective endocarditis, hepatitis, meningitis & encephalitis .

CHAPTER XVII

DIAGNOSTIC CYTOLOGY

This examination of fluids or aspirated material for their cellular content and other elements. It is a rapid, easy, cheap and reliable technique in pathological diagnosis.

TYPES OF CYTOLOGY SAMPLES:

- 1-**Body fluids** e.g. a)Urine b)CSF c) Effusions as pleural & pericardial effusions, ascites, synovial effusions c)Cystic fluid e.g. ovarian cysts, mammary cysts
- 2-**Sputum**
- 3-**Discharge** e.g. nipple discharge, conjunctival discharge.
- 4-**Lavage fluid** e.g. bronchial lavage, bladder and/or pelviureteric wash.
- 5-**Brush cytology** e.g. brush of common bile duct, bronchial and gastric brush.
- 6-**Touch imprint cytology** e.g. imprint of the cut surface of an excised lymph node or excised breast tumor, testicular imprint...
- 7-**Fine needle aspiration cytology (FNAC) or fine needle aspiration biopsy (FNAB)** from superficial lesions such as breast masses, lymph nodes, thyroid & superficial soft tissue tumors or from deep sites (as prostate, liver, kidney, mediastinum, lung, retroperitoneal... etc) using US-guided (ultrasound) or CT-guided techniques.
- 8-**Cervicovaginal smears (PAP-smears):** These smears are stained with Papanicolaou stain (PAP).
- 9-**Bone marrow aspirate**

UTILITY

- 1-**Pathological Diagnosis** e.g. breast cancer can be diagnosed by FNAC & lung cancer by sputum cytology
- 2-**Screening** for detection of premalignant or early malignant lesions e.g. PAP smears, urine & sputum examination
- 3-**Follow up** e.g. urine cytology of patients treated from cancer bladder

TECHNIQUES

- 1-**Centrifugation** of fluids by ordinary centrifuge or by cytospin and using the sediment in processing cytology films on glass slides. Part of the sediment may be fixed in formalin, paraffin embedded (cell block) and used to process paraffin sections (similar to biopsy samples).
- 2-**Fixation** in ethyl alcohol (95%) or cytofix spray.
- 3-**Staining** a)Routine stains as Papanicolaou (PAP), hematoxylin and eosin, toluidine blue & Geimsa; the later is a good stain of the nuclei. B)Special stains as PAS (for glycogen, mucus, fungi), silver stains (for fungi and some protozoa & immunohistochemical stains

SAMPLE DESCRIPTION

Gross description : Volume and colour

Microscopic description: Using low power, high power & sometimes very high power (oil immersion lens) to determine type of cells (inflammatory, benign, malignant ... etc)

DIAGNOSIS REPORTING

1-Normal cytology with no abnormality

2-Inconclusive: cytology → repeat cytological examination and /or lesion biopsy

3-Abnormal cytology e.g. infection, benign cells, malignant cells, dysplastic cells ... etc.

The main cytological differences between benign and malignant cells in cytology are :

- | |
|--|
| <p><u>Nuclei of malignant cells show</u></p> <ol style="list-style-type: none">a)anisonucleosis (different sizes and shapes)b) high N/C ratioc)abnormal chromatind) irregular nuclear membranese)sometimes prominent nucleoli <p><u>Nuclei of benign cells:</u></p> <ol style="list-style-type: none">a)regularb)normal N/C ratio c)fine chromatind) rounde) inconspicuous nucleoli |
|--|

4-Suspicious cytology (malignancy is suspected but not concluded)→ biopsy.

GENERAL PATHOLOGY

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